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MODERN THEORIES
OF
ORGANIC CHEMISTRY

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ORGANIC CHEMISTRY

BY

H. B. WATSON, D.Sc. (WALES), F.I.C.
HEAD OF THE DEPARTMENT OF CHEMISTRY AT THE CITY OF
CARDIFF TECHNICAL COLLEGE
FORMERLY LECTURER IN CHEMISTRY AT THE
UNIVERSITY COLLEGE OF NORTH WALES
BANGOR

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PREFACE TO THE SECOND EDITION

ANY treatise dealing with a rapidly advancing subject inevitably loses its value unless it keeps step with progress. The present work is no exception; it was first published in November 1937, and a thorough revision has now been necessary in the preparation of this second edition. The progress of theoretical organic chemistry during a period of some three years—and years of unutterable tragedy in many spheres—has been such as to demand additions and modifications throughout the book.

The work of revision has also provided an opportunity of making certain alterations and rearrangements which, it is hoped, may give increased clarity and usefulness. Some subjects, too, have been treated rather more fully than before.

It is again a pleasure to record my appreciation of the helpful advice and suggestions offered by numerous friends. I am indebted to Professor Ingold and to the publishers of *Nature* for permission to insert the rather long quotation on pages 13 to 15, and my thanks are also due to the officials of the Oxford University Press for their continued helpfulness and consideration.

H. B. W.

CARDIFF, *April* 1941.

PREFACE TO THE FIRST EDITION

PROFESSOR G. N. LEWIS'S conception of the sharing of one or more electron pairs by two atoms gave a new and illuminating picture of the bonds which link carbon atoms into chains and rings, and set organic chemists the task of interpreting the reactions of carbon compounds of various types in terms of the electronic structures of the molecules. The problem was attacked ten to fifteen years ago, mainly by Professors Lapworth, Robinson, and Ingold. Considerations of the chemical evidence in the light of the electronic theory of valence led to results of great value, and it now became possible to express many of the earlier ideas in more definite and elegant language. Then followed the very fruitful alliance of organic chemistry with physics and mathematics, and a much clearer view *of the principles underlying the behaviour of organic compounds* has been opened up by the aid of modern physical methods of investigation, and of Planck's Quantum Theory and Schrödinger's Wave Mechanics. Some idea of the progress which the past fifteen years have witnessed may be obtained by comparing the conceptions set out in Henrich's excellent treatise dealing with Theories of Organic Chemistry, English translation dated 1922, with papers upon similar topics published in 1937.

In this volume an attempt is made to present the modern viewpoint in a coincise and simple form, and to show how the new conceptions have followed logically from the earlier views. A brief and very elementary account of the physical foundations of the subject is followed by the development of the main theme of the book, viz. the application of the electronic theory to the reactions of organic compounds, and by a description of some of the better known phenomena (such as addition and substitution reactions, tautomeric changes, molecular rearrangements, and the stability of free radicals) in terms of modern ideas. An account of some of the recent developments in stereochemistry is also included.

Every effort has been made to avoid cumbersome detail, and to arrange and present the material in such a manner that it may be easily understood and assimilated by students reading for initial degrees and by those whose interests lie mainly in other fields of chemistry. The book has been based, in fact, upon lecture courses given to undergraduates over a number of years. It is inevitable that much matter of importance should be omitted from a brief and elementary survey of this type; a complete account of all aspects of theoretical organic chemistry would occupy many volumes of this size. The object of the present work is to give a general picture of the field rather than a detailed account of any particular section. The references to treatises and scientific journals (which do not claim, of course, to constitute a complete bibliography) will assist those who so desire to make a further and more comprehensive study of any sections in which they may be particularly interested. The references to journals are given in the form employed in the British Chemical Abstracts.

The many books and original memoirs which I have consulted during the preparation of the manuscript are referred to in their appropriate places. It is fitting, however, that special mention should be made of two of these which I have found more than usually helpful and illuminating; these are Professor Sidgwick's *Electronic Theory of Valency* (1927) and Professor Ingold's 'Principles of an Electronic Theory of Organic Reactions' published in *Chemical Reviews*, 1934.

I wish to take this opportunity of acknowledging my indebtedness to the late Professor Kennedy Orton; if any merit be found in this work, it must be ascribed first and foremost to his inspiring influence in early days. Then, I owe a great debt to Professor Ingold, who has read almost the whole manuscript; his helpful advice and suggestions have been of the utmost value. My thanks are also due to Professor Sidgwick and Professor Hinshelwood for their kind interest and assistance. Dr. E. D. Hughes, of University College, London, and my colleagues Dr. Dippy and Dr. Evans of the Cardiff Technical College have read the work in manuscript, and their suggestions, both those actually relating to the present work and those made during frequent discussions over a period of some years, have always proved helpful and stimulating. Professor Sugden and Professor Wardlaw have also given me assistance in portions of the work where their advice is of particular value.

I am also indebted to the Chemical Society, the Society of Chemical Industry, and the authors from whose papers several diagrams have been reproduced, for permission to include these illustrations.

Finally, it is a pleasure to express my appreciation of the efficient and considerate manner in which the officers of the Oxford University Press have carried out their share of the task, and to record my debt to my wife, whose encouragement and help in matters nonchemical have been no less valuable than the assistance of a more definite character which I have received from fellow chemists.

H. B. W.

CARDIFF, *July* 1937.

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I

THEORIES OF CHEMICAL COMBINATION

THE ultimate particles of matter were described by Sir Isaac Newton as being 'solid, massy, hard, impenetrable, . . . incomparably harder than any porous body composed of them, even so very hard as never to wear or break in pieces', and John Dalton's famous contribution to science in 1803 consisted in the application of this ultimate particle or atom to the explanation of chemical processes. With the work of these great pioneers as its foundation, there has developed the conception of an atom of complex design, with electrons governed by quantum laws and a nucleus which is itself composite—in striking contrast with the Newtonian miniature cannon-ball. Our present views of molecular structure are equally distant from those of Lavoisier, who regarded inorganic and organic compounds as the oxides of simple and compound radicals respectively, and the long, long trail of investigation and progress, of experiment and theory, which has led from the old to the new, forms one of the most intriguing chapters in the history of science.

In the opening years of the nineteenth century the electrolytic decomposition of water (Nicholson and Carlisle, 1801), of aqueous solutions of salts (Berzelius and Hisinger, 1803), and of fused alkalis (Davy, 1807) was achieved, and upon these new discoveries Berzelius based his Dualistic Theory of Combination (1812). This hypothesis, which actually represented a development of the views of Davy, ascribed the union of atoms to opposite electrochemical characters, and it was not incompatible either with Lavoisier's original conceptions or with the Radical Theory as extended through the researches of Gay-Lussac, Liebig, Wöhler, Bunsen, and others. In the meantime, the barrier between organic and inorganic chemistry had been broken down by Wöhler's synthesis of urea (1828), and, commencing with Liebig's demonstration of the identity in composition of cyanic and fulminic acids, a number of examples of isomerism had been discovered. Thus far, however, there was no experimental evidence which was definitely contrary to a dualistic view.

But in 1839 Dumas found that three *electronegative* chlorine atoms could replace three *electropositive* hydrogens of acetic acid without change in the fundamental nature of the compound; the 'type' was unaltered. This discovery was the main cause contributing to the overthrow of dualism and the replacement of the conceptions of Berzelius by a unitary theory, the chief exponents of which were Dumas, Laurent, and Gerhardt, and which was elaborated in 1853 as Gerhardt's Theory of Types.

At the same time, the idea of valency or saturation-capacity was developing. Williamson (who is famous chiefly for his researches on the ethers) pointed out, in 1851, that different groups might replace different numbers of hydrogen atoms, and in the following year this conception was extended to atoms by Frankland, as the result of his study of the organo-metallic compounds. The suggestions thus made by Williamson and Frankland led to the Structural Theory of Kekulé and Couper, and ultimately to the modern representation of organic compounds with chains and rings of carbon atoms. In 1874 the Structural Theory was extended to three dimensions by van't Hoff and Le Bel, who laid the foundations of modern stereochemistry.

> 'The structural theory is of extreme simplicity. It assumes that the molecule is held together by links between one atom and the next: that every kind of atom can form a definite small number of such links: that these can be single, double or triple: that the groups may take up any position possible by rotation round the line of a single but not round that of a double link: finally that with all the elements of the first short period, and with many others as well, the angles between the valencies are approximately those formed by joining the centre of a regular tetrahedron to its angular points. No assumption whatever is made as to the mechanism of the linkage.
>
> 'Through the whole development of organic chemistry this theory has always proved capable of providing a different structure for every different compound that can be isolated. Among the hundreds of thousands of known substances, there are never more isomeric forms than the theory permits.'[1]

So successful was the Structural Theory that there was a strong tendency for the electrochemical views of Berzelius to be completely forgotten; the forces binding atoms together, whatever might be their origin, were now regarded as non-electrical in nature. The contrast between the two theories arose, of course, from the fact that Kekulé dealt with organic compounds while Berzelius had built up his views in relation to acids, bases, and salts. In spite, however, of the dominating influence of the Structural Theory, electrochemical ideas persisted in the minds of a minority of scientists, and a connexion between valency and electrical charges was postulated by Helmholtz in his well-known Faraday Lecture of 1881,[2] and rendered still more probable by the success of the Ionic Dissociation Theory of Arrhenius (1887).

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[1] Sidgwick, Presidential Address to the Chemical Society, 1936: *J.C.S.* 1936, 533.

Five years later, in an endeavour to represent the so-called 'molecular compounds' or 'compounds of higher order' which defied all known rules of valency, Werner postulated yet another type of linkage.[3] He spoke of atoms or groups as being 'co-ordinated' with a central atom, their number bearing no relationship to the periodic group of the element which, as Mendeléeff had pointed out, normally governs the valency; the 'co-ordination number' of an atom was quite distinct from its 'valency' as usually defined. Chemistry was thus left with the electrochemical, structural, and co-ordination theories, each satisfactory in its own sphere, but none capable of embracing the whole of the facts.

Now came four discoveries of the first importance, each of which was destined to play a leading part in the development of the theory of atomic and molecular structure. They were: the discovery of the inert gases by Rayleigh and Ramsay (1894), of X-rays by Röntgen (1895), of radioactivity by Becquerel (1896), and of the electron by Sir J. J. Thomson (1897). It soon became evident that the electron is a constituent of every atom,[4] and it was natural that attempts should be made to visualize valency and chemical combination in terms of this unit of negative electricity. Among the earlier electronic theories of valency were those of Sir J. J. Thomson,[5] Falk and

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[2] *J.C.S.* 1881, **39**, 302. In the same lecture Helmholtz pointed out how Faraday's Laws indicated that electricity, like matter, is discontinuous ('atomic') in nature.

[3] See Werner, *New Ideas on Inorganic Chemistry* (Longmans, 1911). Confirmation of Werner's theory, by the preparation of the stereoisomerides which it predicted, was obtained in 1911 (see Chapter XVI).

[4] This conclusion was based mainly upon observations of the liberation of electrons (always identical in charge and mass) by the passage of electric discharges through gases at low pressures, by the raising of a metal to a sufficiently high temperature (thermions), by the action of ultra-violet and even visible light upon metals and to a lesser extent non-metals (photoelectric effect), and in radioactive disintegrations (β-rays). It was confirmed by the quantitative study of the Zeeman effect (the splitting of spectral lines by a magnetic field, Zeeman, 1896).

[5] *Electricity and Matter*, 1907.

Nelson,[6] and Fry;[7] the clear definition of chemical combination in electronic terms did not emerge, however, until 1916.

The necessity of accounting for the mass and the electrical neutrality of the atom, together with the results of Geiger and Marsden's experiments upon the scattering of α-particles, led Sir Ernest Rutherford to formulate his Nuclear Atom model (1911) in which a positively charged nucleus, responsible for practically the whole of the mass of the atom, was surrounded by a distribution of electrons, and Bohr's application of the Quantum Theory to this atom model in 1913 enabled him to make his distinguished contribution to the interpretation of line spectra. The work of Moseley (1913–14) upon the X-ray spectra of the elements made clear the fundamental character of the atomic number (the integer which denotes the position of the element in the natural sequence, i.e. the periodic table), and this was identified with the number of units in the positive nuclear charge,[8] and therefore, since the atom is electrically neutral, with the number of extranuclear electrons.

The early calculations of Sir J. J. Thomson had indicated that these electrons must be arranged in layers or groups; in Bohr's theory they occupy different 'energy levels' denoted by quantum numbers. On the basis of the physical properties and the periodicity of the elements, Bohr has worked out the probable groupings of electrons in the various atoms,[9] and his scheme is in agreement with that of Bury which was based on chemical properties.[10] As the atomic number increases from unity upwards, a quantum group of two electrons (in helium) and then two quantum groups of eight (in neon and argon) are completed. In the transitional elements of the long periods, the last group but one expands to eighteen, and then at the end of these periods an outermost group of eight is again formed. In the elements of the rare earths the last group but two increases to thirty-two electrons. The structures given in the table on the opposite page exemplify the general principles upon which the electronic arrangements are based.

It will be seen that eight electrons are assigned to the outermost group in all the inert gases except helium, which has two, and an

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[6] *J. Amer. Chem. Soc.* 1910, **32**, 1637; 1913, **35**, 1810; 1915, **37**, 1732.

[7] See Fry, *The Electronic Conception of Valence* (Longmans, 1921).

[8] The actual demonstration was given by Chadwick, *Phil. Mag.* 1920, **40**, 734.

[9] *Theory of Spectra and Atomic Constitution* (Cambridge, 1922).

[10] *J. Amer. Chem. Soc.* 1921, **43**, 1602.

Number of Electrons in Quantum Groups

Quantum number	*1*	*2*	*3*	*4*	*5*	*6*
H	1					
He	2					
Li	2	1				
C	2	4				
F	2	7				
Ne	2	8				
Na	2	8	1			
Cl	2	8	7			
A	2	8	8			
K	2	8	8	1		
Ca	2	8	8	2		
Sc	2	8	9	2		
Zn	2	8	18	2		
Kr	2	8	18	8		
Xe	2	8	18	18	8	
Ba	2	8	18	18	8	2
La	2	8	18	18	9	2
Ce	2	8	18	19	9	2
Lu	2	8	18	32	9	2
Hg	2	8	18	32	18	2
Rn	2	8	18	32	18	8

electronic group in an uncombined atom exceeds eight only when it is not the outermost.[11] The number of electrons occupying the outside group of each atom (excluding the transitional elements) is shown below:

Number of Electrons in Outermost Group

Number of Electrons	*1*	*2*		*3*	*4*	*5*	*6*	*7*	*8*
Hydrogen Period	H	He							
First Short Period	Li	Be		B	C	N	O	F	Ne
Second Short Period	Na	Mg		Al	Si	P	S	Cl	A
First Long Period	K	Ca	Transitional Elements	Ga	Ge	As	Se	Br	Kr
Second Long Period	Rb	Sr		In	Sn	Sb	Te	I	Xe
Third Long Period	Cs	Ba		Tl	Pb	Bi	Po	..	Rn
Last Period	..	Ra							

The chemical properties of the element are determined mainly by these electrons in the outermost group, which are therefore termed

---

[11] Langmuir (*J. Amer. Chem. Soc*, 1919, 41, 868) had previously suggested arrangements in which the outermost electronic groups of the inert gases had 2, 8, 8, 18, 18, and 32 electrons respectively.

'valence electrons'. Periodicity is clearly due to a recurrence of the same number in this group. In the transitional elements the last group but one is in process of expansion to eighteen, and under suitable conditions the electrons of this group may function as valence electrons in addition to those of the outside group. The frequent variations in valency shown by these elements are thus accounted for.

The complete inactivity of the rare gases indicates extreme stability of their atoms, and it is logical, therefore, to ascribe chemical combination to the tendency of other atoms to take up the inert gas configuration, with its outermost group of eight electrons. This may be achieved by the complete transference of one or more electrons from one atom to another, a process which, in the early electronic theories referred to above, was assumed to occur in the formation of *all* linkages. In 1916 Kossel showed how this conception of complete electronic transference provides a satisfactory picture of the ions which are characteristic of electrolytes.[12] It obviously does not explain the binding of atoms in the molecules of non-ionizable substances, and the further problem presented by these compounds found a solution in G. N. Lewis's postulate of the sharing of a pair of electrons by two atoms.[13] The two types of linking are designated '*electrovalent*' and '*covalent*' respectively, these terms being due to Langmuir,[14] and the distinction between them has been emphasized by the results of determinations of the crystal structures of electrolytes and non-electrolytes.[15]

The incorporation within the electronic theory of Werner's concept of co-ordination is based on the suggestion, made by G. N. Lewis, that an atom having one or more unshared pairs may contribute *both* electrons to its bond with another atom, provided that the latter is able to accommodate a further pair in its valence group. This view is applicable to the ammonium and borofluoride ions, the metallic ammines, and a vast number of other compounds, and the type of linkage here postulated has been discussed fully by Sidgwick[16] who terms it the '*co-ordinate*' bond. Important information regarding the presence of co-ordinate bonds in certain compounds has been obtained by the application of Sugden's Parachor.[17] In comparisons of molecular volumes it had been customary to employ values obtained either at a fixed temperature (Traube) or at the boiling-points of the liquids concerned (Kopp). Since boiling-points are approximately corresponding temperatures (equal fractions of the critical temperature), Kopp's values were long regarded as comparable, but Sugden points out that the most important factor to be considered is the internal pressure, which is of great magnitude, and is measurable with a good degree of approximation by the surface tension to which it gives rise. From MacLeod's equation for the effect of temperature upon surface tension,[18] viz. $\gamma^{1/4}/(D-d) = \text{const.}$ (where γ is surface tension and D and d the densities of liquid and vapour respectively, d being negligible at ordinary temperatures in comparison with D), Sugden deduces the expression $\gamma^{1/4}M/D = P$, where M is the molecular weight, and the constant P is termed the Parachor. The values of P for different liquids provide a measure of the relative molecular volumes under such conditions that the surface tension (and therefore the internal pressure) has a uniform value, i.e. the conditions which are regarded as comparable. For a given compound, P has proved to be the sum of a series of terms, each referring to a particular atom or linkage, and a consideration of some 200 liquids enabled Sugden to compute atomic and constitutive parachors. A striking result which emerged from this work was the discovery that linkages conventionally written as 'double bonds' are of two types; the C=C, C=N, C=O, C=S, and N=O bonds lead to an increase of 23·2 units in the parachor, while the 'double' bonds between oxygen and phosphorus or sulphur in derivatives of phosphoric, sulphurous, and sulphuric acids decrease its value by a small amount averaging 1·6 units. Linkages of the former type are identified with four-electron or non-polar double bonds, and those of the latter type are interpreted as co-ordinate bonds (they have been referred to by Sugden as 'semipolar double bonds' and by Lowry as 'mixed double bonds'[19]).' Examination of a number of compounds containing the nitro-group led to the conclusion that one of the oxygens is linked by a four-electron bond and the other by a

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[12] *Ann. Physik*, 1916, **49**, 229.

[13] *J. Amer. Chem. Soc.* 1916, **38**, 762; *Valence and the Structure of Atoms and Molecules* (Chemical Catalog Co., New York, 1923).

[14] Ref. 11. The characteristic properties of electrovalent and covalent compounds are discussed fully by Sidgwick, ref. 16.

[15] Sir W. H. and W. L. Bragg, *The Crystalline State*, G. Bell & Sons, 1933.

[16] *The Electronic Theory of Valency* (Clarendon Press, 1927).

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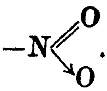
[17] Sugden, *The Parachor and Valency* (G. Routledge & Sons, 1930). *J.C.S.* 1924, **125**, 1177; 1925, **127**, 1525.

[18] *Trans. Faraday Soc.* 1923, **19**, 38.

[19] *J.C.S.* 1923, **123**, 822.

co-ordinate bond, and the group was therefore written  $-\mathrm{N}\begin{smallmatrix}/\!\!/\mathrm{O}\\ \searrow\mathrm{O}\end{smallmatrix}$.[20] Such a formula is in harmony with the fact that nitrogen never forms more than four covalent linkages, the fifth valency of 'pentavalent' nitrogen always being an electrovalency. Stereochemical evidence further indicates the presence of co-ordinate bonds in compounds such as amine oxides, sulphinic acids, and sulphoxides.[21]

In all the compounds referred to above, the number of co-ordinate bonds is just that required to preserve the octet (group of eight valence electrons) of the central atom; for this and other reasons Sugden has suggested that the octet is the maximum valence group, and that, where more than four atoms are covalently linked to a central atom, bonds of one electron are present. Much evidence has been put forward by Sidgwick, however, in favour of the view that the valence group may expand beyond eight. His Covalency Rule[22] limits the covalency of an element in accordance with the *period* in which it stands in the Periodic Table, the following covalency maxima being postulated: H, 4 electrons;[23] elements of first short period (Li to F), 8 electrons; elements of second short period (Na to Cl) and first long period (K to Br), 12 electrons; elements of higher atomic number, 16 electrons.

The above summary will serve to indicate how the electrochemical, structural, and co-ordination theories of chemical combination have been included in one comprehensive electronic theory of valency. Nothing has been said as yet, however, regarding the physical interpretation of the electrovalent and covalent bonds. It is evident that the force acting between the ions of an electrolyte is the attraction of opposite charges; the bond is of an electrostatic character. The manner in which atoms are bound by electron sharing, however, presents a far more complex problem, which is now being approached from the standpoint of the new Quantum or Wave Mechanics. Of recent years, too, the electronic theory of valency has been extended by the introduction of the theory of Mesomerism, without which it was unable to embrace all the observed phenomena; this also has its foundations in the quantum theory.

The recent development of physical methods of investigation has yielded much information regarding important details such as the lengths of covalent bonds (interatomic distances), the proportions in which the electrons are shared, the angles between linkages, and the strengths of the bonds.

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[20] See further, p. 59.

[21] See Chap. XVI.

[22] Ref. 16. *Ann. Reports*, 1933, **30**, 110.

[23] On 'two-covalent' hydrogen, see further, p. 22.

> 'We have applied to their investigation a whole series of physical methods, based on the examination of the absorption spectra in the infra-red, the visible, and the ultra-violet, and of the Raman spectra: on the measurement of specific heats and heats of combustion, of the dielectric properties, and of the scattering of X-rays and electron waves, as well as on the study of chemical dynamics: to mention only the most important. To Kekulé the links had no properties beyond that of linking; but we now know their lengths, their heats of formation, their resistance to deformation, and the electrostatic disturbance which they involve. Throughout all this work the starting-point has always been the structural formula in the ordinary organic sense. There is no better example of the effect of new discoveries in giving new meaning to a theory while they leave the truth of the theory unaffected, and of the way in which modern research, instead of being content with evidence of one kind, as were the older organic chemists with that of chemical reaction, draws its material from every side, and from every branch of chemistry and physics.'[24]

Like the theory of valency itself, these new physical methods are dependent upon the quantum theory, and a short and elementary account of the conceptions underlying this theory and its applications to the problems of chemistry is therefore given here.

Applications of the Quantum Theory[25]

In 1900 Planck found that the experimental facts concerning thermal radiation, which could not be harmonized with the laws of classical mechanics, received a satisfactory interpretation on the basis of the postulate that the emission of energy occurred in definite small elements or 'quanta', the magnitude of which was given by the product of the frequency and a constant h; $E = h\nu$. This discovery marks the origin of the view that energy, like matter and electricity, is discontinuous or 'atomic' in nature. The quantity h is now known as Planck's Constant, and is a universal constant like the velocity of light or the charge on the electron. Five years later, Einstein applied Planck's theory to the interpretation of the photoelectric effect, i.e. the emission of electrons by a large number of metals and some gases under the influence of X-rays, ultra-violet light, and even visible light. He was able to interpret the observed facts by postulating light quanta or photons, the magnitude of which depended solely upon the colour (frequency). In Einstein's hands, too, the quantum theory proved capable of yielding a law which correctly represented the experimental observations (Nernst and others) of the variation of specific heats with temperature, this law being perfected by Debye in 1912. The value of the Quantum Theory had thus been demonstrated in three directions when, in 1913, Bohr applied it to the Rutherford Atom and achieved remarkable success in the interpretation of the line spectrum of hydrogen. Classical mechanics and electrodynamics could not account for the stability of the atom as represented by the nuclear model. If the electrons were assumed to be at rest, some wholly unknown law of force was necessary;[26] if they circulated round the nucleus, energy would be radiated (since their velocities would continually change in direction), and the atom would thus suffer spontaneous destruction. Bohr now postulated that, while the electron actually circulates in an orbit in accordance with the inverse square law, only certain so-called 'stationary' orbits are possible, these being defined by the condition that the electron must possess a whole number of quanta of energy, i.e. $E = nh\nu$. He made the further assumption that no energy is radiated while the electron remains in one of these orbits. The whole number n was termed the 'quantum number' of the orbit, and Bohr thus introduced the conception of different states of the atom associated with different amounts of energy, the energy levels being defined by the quantum numbers. It may here be pointed out that, although the modern quantum theory has relinquished the conception of precise orbits, the energy levels retain their significance. Bohr's final postulate was that, under the influences which give rise to the emission of radiation, the electron is drawn out into a higher energy level, and its return (by a 'quantum jump') to the lower level gives rise to radiation of frequency $\nu = (E-E')/h$ where E and E' represent its energies in the two levels. On the basis of these postulates he calculated the frequencies of the lines in the hydrogen spectrum (circular orbits being assumed) as

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[24] Sidgwick, *J.C.S.* 1936, 533.

[25] See Pauling and Wilson, *Introduction to Quantum Mechanics* (McGraw-Hill Book Co., New York, 1935). A simple account of the applications of the Quantum Theory to Chemistry is given by Haas, *Quantum Chemistry* (Constable, 1930), and the wave-mechanical treatment of chemical problems is described by Pauling, *The Nature of the Chemical Bond* (Cornell University Press, 1939), and chap. 22 of Gilman's *Organic Chemistry*, vol. 2 (John Wiley, New York, 1938). References to the original literature are given in these works, and are not repeated here.

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[26] Such a law was postulated by Sir J. J. Thomson, *Phil. Mag.* 1921, **41**, 510.

$$\nu = \frac{2\pi^2 me^4}{h^3}(1/n_1^2 - 1/n_2^2) = R(1/n_1^2 - 1/n_2^2)$$

(where m and e represent respectively the mass and charge of the electron, h is Planck's constant, and n_1 and n_2 are quantum numbers). This expression is identical with the Balmer formula for the line spectrum of hydrogen in the visible, ultra-violet, and infra-red regions, and the term R, calculated from the known values of the constants involved, was in quite good agreement with the experimentally determined value of the Rydberg Constant. Still better agreement was obtained when allowance was made for the motion of the nucleus, and the 'fine structure' of the lines was accounted for by Sommerfeld's postulate (1918) of elliptical in addition to circular orbits. The Bohr-Sommerfeld theory was thus remarkably successful in interpreting the line spectrum of hydrogen, and also that of ionized helium (spark spectrum). The spectra of other elements resemble that of hydrogen sufficiently closely to indicate that an interpretation might be found on similar lines, but the general problem of determining the orbits of more than one electron remained insoluble. Even the helium atom (with two electrons) and the simplest of all molecules, that of hydrogen, could not be dealt with by Bohr's method, the usefulness of which was thus very limited. Moreover, the selection of the stationary states was purely arbitrary, and the absence of any radiation when the electron circulated in one of these orbits found no explanation. The Bohr-Sommerfeld theory was clearly not altogether satisfactory.

From 1924 onwards a new line of attack upon the problems of atomic and molecular structure has been developed; it is the counterpart of a dual procedure employed of late years in the study of optical problems. The long struggle between the corpuscular and the undulatory theories of light is famous in the history of physics; in the first half of the nineteenth century the latter, as expounded by Fresnel and Young, gained a complete triumph over the Newtonian conception. In 1905, however, Einstein postulated light quanta in order to interpret the photoelectric effect; both this effect and its converse (the production of radiation when electrons impinge upon matter as in X-ray tubes) proceed as if the radiation were composed of small discrete units. Simultaneously with the photoelectric effect there occurs the Compton Effect, first observed in 1923; a portion of the incident radiation is scattered with a reduced frequency, and this is ascribed to the collision of a quantum with an electron, to which the energy is partially transferred with the production of a quantum of lower energy, and therefore lower frequency since $E = h\nu$. It is necessary, indeed, to postulate the existence of light quanta which obey the laws of collision between elastic bodies. Allied to the Compton Effect is the phenomenon observed by Sir C. V. Raman in 1928;[27] a quantum here encounters a molecule, atom, or ion, the energy level of which is raised with a corresponding reduction in the energy (and hence frequency) of the quantum itself.

Einstein's postulate of light quanta has thus been verified in several ways, with the result that of recent years a partial return to the corpuscular conception of light has taken place. Although, however, properties characteristic of matter can be ascribed to light, the undulatory theory still retains its value, and is necessary for the understanding of phenomena such as interference, diffraction, polarization, reflection, and refraction. The two points of view can be harmonized by assuming that the square of the amplitude of vibration (which, on the undulatory theory, is a measure of the intensity) gives the probability that a quantum is situated at a given spot. Either approach may be used, according to the requirements of the problem under consideration.

In 1924 de Broglie suggested the reversal of the process which had proved so successful in optics, by extending to matter the undulatory characters of light, and this procedure has received justification in observations of the diffraction of electrons, similar to that of X-rays, by metals and other substances.[28] de Broglie's suggestion was followed by the development of Schrödinger's equation in 1926. It has the form of the general equation for a three-dimensional vibrating system; the vibrating quantity is written ψ, and its frequency is E/h. The new viewpoint does not remove the significance of the electron and the atom as definite individual particles, but the *behaviour* of electronic systems is described in terms of a wave function. Otherwise expressed, the laws which govern atomic phenomena can be represented by differential equations of the same form as those which are normally applicable to wave motion, and in place of the orbits of the Bohr theory we are provided with the conception of the electrons moving in a manner defined by such an equation. The wave-mechanical view of matter is completely analogous to the method employed in treating optical problems; it provides a quantity the square of which represents the probability that the electron is situated at a given point.

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[27] See Chap. IV.

[28] e.g. Davisson and Germer, 1927; G. P. Thomson, 1928. See further Section 3 of Chap. IV.

Schrödinger's equation is expressed in terms of energy, and, in accordance with a general feature of differential equations of this type, there are characteristic values (eigenvalues) of the energy for which, and for which alone, the equation has solutions which are finite, continuous, and single-valued. These eigenvalues actually represent the energy levels of the Bohr theory. Bohr's arbitrary selection of the stationary states thus becomes a deduction from the wave equation, the energy states of the atom being determined by the eigenvalues.

Quantum-Mechanical Resonance. To the organic chemist the main importance of these new developments lies in the phenomenon of Resonance, the discovery of which has been described as the most important development in structural chemistry since the days of van't Hoff.[24] The existence of resonance is deduced from the equations of wave mechanics, and could not have been predicted otherwise; nevertheless the main conceptions can be stated in simple language.

Quantum-mechanical resonance is best understood by reference to the mechanical illustration of two equal pendulums connected at their points of suspension (e.g. suspended from the same flexible string). The motion of each is then modified by the other, and if their phases are the same or exactly opposed they will oscillate with a frequency which is either less or greater than the frequency of either when oscillating independently. The observed effects are clearly described in the following quotation:[29]

'In order to appreciate the significance of resonance in the theory of valency, it is useful to recall the nature of resonance in vibrating mechanical systems. The simplest example is that of two like pendulums hung from the same stretched string. If one pendulum is given a displacement, its interaction with the string causes the vibratory motion gradually to become transferred to the second pendulum, after which it travels back to the first (Fig. 1). This motion is obviously not simple harmonic, but it can be shown to be a mixture of two simple harmonic motions. One of these occurs alone if we start the pendulums with equal amplitudes in phase; the frequency $\nu-\epsilon$ is then a little less than the frequency ν of either uncoupled pendulum, because the two pendulums when swinging in phase deform the supporting string in mutually accommodating ways and this lowers the restoring forces. The other simple harmonic motion occurs

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[29] Ingold, *Nature*, **1938**, **141**, 314.

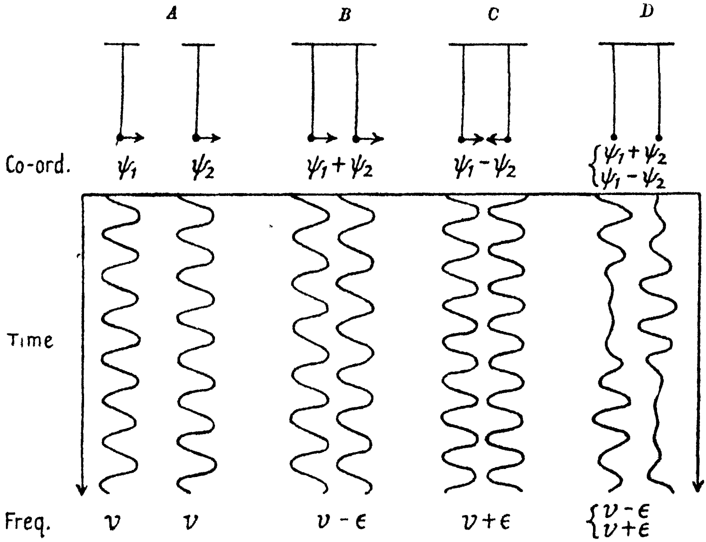
A
B
C
D
Co-ord.
ψ_1
ψ_2
$\psi_1+\psi_2$
$\psi_1-\psi_2$
$\begin{cases}\psi_1+\psi_2\\ \psi_1-\psi_2\end{cases}$
Time
Freq.
ν
ν
$\nu-\epsilon$
$\nu+\epsilon$
$\begin{cases}\nu-\epsilon\\ \nu+\epsilon\end{cases}$

FIG. 1. Mechanical resonance: time-graphs illustrating the behaviour of uncoupled and coupled pendulums.

when we start the pendulums with equal amplitudes in opposite phase; the frequency $\nu+\epsilon$ is now a little greater than that of the uncoupled pendulums because of the opposing actions on the string. When we start the pendulums with any arbitrary amplitudes and phase difference, the two simple harmonic motions occur together, and the "beats" arising from their differing frequencies give rise to the complicated motion described.

'If ψ_1 and ψ_2 are the co-ordinates measuring the displacements of the two pendulums, then before coupling, each co-ordinate was associated with a definite frequency ν, but after coupling neither co-ordinate has any definite frequency. On the other hand, the linear combination $\psi_1+\psi_2$ has the frequency $\nu-\epsilon$, whilst the combination $\psi_1-\psi_2$ has frequency $\nu+\epsilon$. We may say that the mutual perturbation or "resonance" has replaced the former co-ordinates of periodic motion (ψ_1 and ψ_2) by two independent linear combinations ($\psi_1+\psi_2$ and $\psi_1-\psi_2$), and has split the original coincident frequency (ν) into two frequencies, one greater and one less than the original.

'In Fig. 1, (*A*) represents the uncoupled equivalent pendulums. Their displacement co-ordinates are ψ_1 and ψ_2, and their motion is periodic, each pendulum having the frequency ν. (*B*) and (*C*) illustrate the only two sets of conditions in which the pendulums, when coupled, can undergo singly periodic motion. In mode (*B*) the pendulums are started with equal amplitudes in phase, and they then keep in phase; the displacement co-ordinate of the coupled system is thus $\psi_1+\psi_2$. As the time-graph shows, the period is a little longer, and therefore the frequency, $\nu-\epsilon$, is a little smaller, than for a single uncoupled pendulum. For mode (*C*) the pendulums must be started with equal amplitudes in opposite phase; they then remain in opposite phase, and accordingly the displacement co-ordinate is $\psi_1-\psi_2$. As illustrated in the time-graph, the period is shorter, and the frequency, $\nu+\epsilon$, greater, than for a single uncoupled pendulum. (*D*) represents the general result of coupling, the amplitudes and phase difference at the commencement of motion being arbitrary. Simple periodicity now disappears, but the motion can be represented as a superimposition of the periodic motions separately represented in (*B*) and (*C*). On account of the small frequency differences produced by the coupling, the superimposition of these periodic motions causes the beat-like alterations of amplitude illustrated in the time-graph. Thus the general effect of the coupling is to replace two identical periodic motions by two other periodic motions, one of increased and one of decreased frequency.'

The phenomenon of quantum-mechanical resonance is analogous to the mechanical resonance described above (although the analogy has its limitations), and Heitler and London[30] have applied the concept to the interpretation of the forces operating in chemical combination. The starting-point of the argument is the principle that the actual structure of any system (in its normal or resting state) is that which, of all possible structures, has the smallest energy and hence the greatest stability. In the equations of wave mechanics, a structure by which a system may be represented is written as a wave function ψ, and if ψ_0 be the correct function for the system in its normal state, then the energy calculated by use of this function will be smaller than that which follows from the use of any other function. Suppose now that a system may be represented by either of two structures, written ψ_1 and ψ_2; it may then also be represented by a function ψ formed by the linear combination of ψ_1 and ψ_2,

$$\psi = a\psi_1+b\psi_2,$$

where *a* and *b* are numerical coefficients (this is a result of the methods of quantum-mechanical theory), and a minimum of energy is possessed by a structure for which the ratio b/a has a certain value. The wave function ψ_0 which gives this energy minimum then represents correctly the normal state of the system, and each of the structures ψ_1 and ψ_2 contributes to this state to an extent determined by the relative values of a and b. The system is said to be in resonance between these structures. The number of contributory structures is not limited to two, and in general

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[30] *Z. Physik*, 1927, **44**, 455.

$$\psi_0 = a\psi_1 + b\psi_2 + c\psi_3 + ...,$$

where the coefficients a, b, c, etc., have the relative values required for the minimum of energy, these values being determined by the relative stabilities of the structures represented by ψ_1, ψ_2, ψ_3, etc.

Heitler and London applied this method to the calculation of the conditions of formation of the simplest of all molecules, that of hydrogen, where the system contains only two nuclei and two electrons; in less simple cases, indeed, the mathematical treatment of the problem can as yet be accomplished only by the aid of considerable approximations.[31]

The energy states of two isolated hydrogen atoms are determined by the solutions of the appropriate wave equation; the electron in either atom moves in accordance with this equation. Actually it remains within a distance of about 0·5 Angström from the nucleus and has a speed of the order of magnitude of 2×10^8 cm./sec., as deduced from the Bohr theory; it does not move in a definite orbit, however, and its speed is variable. If the two atoms come together sufficiently closely, each wave influences the other and new combinations arise (as with the pendulums). Let the nuclei be represented by H_A and H_B and the electrons by e_A and e_B respectively. The two isolated atoms are $H_A e_A$ and $H_B e_B$, but they can combine to form two systems having equal energies; these are $[H_A e_A + H_B e_B]$ and $[H_A e_B + H_B e_A]$. In accordance with the quantum-mechanical principle described above, the normal state of the system will be represented by neither of these structures, but by a combination to which they contribute equally (because their energies are identical); $\psi_0 = a\psi_1 + b\psi_2$ where $a = b$. This combination has a minimum of energy, and it represents therefore a stable system, the hydrogen molecule. This is the wave-mechanical picture of the formation of G. N. Lewis's two-electron covalent bond. The stability of the bond is due to the 'resonance energy' of the process described above; it depends upon the ability of the electrons to 'exchange places', giving two structures which are equivalent energetically and therefore give a resonance state related equally to each.

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[31] This mathematical approach to the problem of molecular structure, which has been developed particularly by Pauling and Slater, is termed the 'Method of Localized Pairs'. Meanwhile, from 1929 onwards, Hund, Lennard-Jones, and Mulliken have attacked the problem somewhat differently, by the 'Method of Molecular Orbitals'. The molecule is treated as a whole; the definite partnership between a given electron and a given nucleus is largely abandoned, and the electrons are regarded as wandering from nucleus to nucleus, their movements being described with reference to *molecular orbitals*. Both the electron pair method and the molecular orbital method are approximations, and the exact truth probably lies intermediate between them; for a concise treatment of both methods, and references to relevant literature, see Penney, *The Quantum Theory of Valency* (Methuen & Co., 1935). The conception of the two-electron bond, as originally put forward by G. N. Lewis, still provides the most useful picture of the molecule for the purpose of interpreting chemical phenomena, however, and will be employed throughout this book.

The final step in the Heitler-London theory of the covalent bond is the application of the Pauli Exclusion Principle. Analysis of the spectra of atoms having more than one electron shows that the lines can be classified in series. Four such series can be distinguished, and are designated principal, sharp, diffuse, and fundamental. The lines of a given series have definite characteristics, and a physical agency such as a magnetic field affects all the lines of one series in a similar manner. Further, the terms representing the energy levels of the alkali metal atoms (which, like hydrogen, consist of a core with one valence electron), when denoted by the expression R/n^2, give values of n which are not integral, and this is interpreted by supposing that the term is actually composite and should be written $R/(n+\alpha)^2$, where α is called the 'quantum defect' and has a constant value throughout one series. The inference is drawn that the electrons can exist in states not accounted for by one quantum number alone, and we thus arrive at the conception of a subdivision of the principal energy levels into a number of subordinate levels. In addition to the *principal* quantum number n, therefore, a second or *azimuthal* quantum number is necessary; this is written l, and is assigned values from 0 to $n-1$. It is conventional to refer to electrons in energy states denoted by the azimuthal quantum numbers 0, 1, 2, and 3 as *s*, *p*, *d*, and *f* electrons respectively, the titles being derived from the initial letters of the spectral series to which they give rise (for example, a transition from an *s* state to a *p* state gives a line in the sharp series, and so on). The limit of $n-1$ for the azimuthal quantum number restricts the 1-quantum group ($n = 1$) to *s* electrons, the 2-quantum group

($n = 2$) to s and p electrons, and the 3-quantum group ($n = 3$) to s, p, and *d* electrons. The possible states of the electron, as indicated by the multiplicity of line spectra, are not yet provided for, however, and two further quantum numbers are necessary. One is the *magnetic* quantum number, having values from $-l$ to $+l$, and the other is the *spin* quantum number. This last describes the direction of spin of the electron, and hence must have two equal and opposite values, which are written $\pm\frac{1}{2}$. A complete description of every electron in the atom is possible in terms of these four numbers. The Pauli Principle states that, in a single atom, no two electrons can exist in exactly the same quantum state, i.e. they cannot coincide in all four numbers, and the number of electrons in a group of given principal quantum number, as calculated from this principle, agrees with that required for the interpretation of the periodic system as suggested by Bohr. In the case of the hydrogen molecule, both electrons belong to each atom, and they must therefore differ in at least one of the quantum numbers. Since they are identical energetically, Heitler and London conclude that they differ in the spin number, and they thus visualize the formation of the covalent bond as the pairing of electrons with opposite directions of spin.

Resonance between different Valence-Bond Structures. Mesomerism. Many molecules can be represented satisfactorily by a single structural formula, which adequately describes their characters. In other cases, however, this is not so; benzene provides the classic example, and the difficulties encountered in ascribing a structural formula to the aromatic nucleus are indicated by the large number of representations which have been suggested from time to time. The conception of quantum-mechanical resonance has thrown much new light upon the structure of molecules of this kind.[32]

In the formation of a covalent bond, the departure from the electronic arrangement characteristic of the free atoms takes place in order that a more stable system may be produced (see preceding section). The completion of this process does not of necessity lead to the most stable structure which the molecule can possess, however, and many molecules can gain additional stability by a further modification of the electronic dispositions. This is the case if the molecule can be represented by two or more structures which differ in the positions of the electrons but not of the nuclei, and which are of the same order of stability (that is, their energies are of the same order of magnitude). The quantum-mechanical principles set out in the previous section then lead to the conclusion that a maximum of stability (minimum of energy) is now possessed by a structure which is a combination of those which can be represented by structural formulae of the ordinary type; it is intermediate between them, and Ingold has therefore named the phenomenon 'mesomerism' ('between the parts'), a term which is perhaps preferable to 'resonance' because the latter tends to convey the impression of a molecule in a state of oscillation, which is not intended. The molecule will normally exist in this condition of maximum stability, for the smaller energy of the 'mesomeric' state leads to its formation in every case where the necessary conditions are fulfilled. The 'unperturbed structures' (i.e. those which are capable of representation by structural formulae) have no existence as states of the molecule, and have been described by Ingold as 'intellectual scaffolding'. If the unperturbed structures have identical energies, the mesomeric state will be related equally to them; otherwise it will approximate more closely to the structure which has the greater stability (lower energy). The difference between the energy of the mesomeric state and that of the structures represented by ordinary formulae is known as the 'energy of mesomerism' (or 'resonance energy', the term used above in connexion with the stability of the hydrogen molecule).

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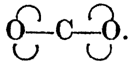
[32] See Pauling, ref. 25. Sidgwick, *Ann. Reports*, 1934, **31**, 37; *J.C.S.* 1936, 533; 1937, 694. Ingold, *J.C.S.* 1933, 1120, *Chem. Reviews*, 1934, **15**, 225.

This energy difference provides a means of detecting mesomerism; the heat of formation of the compound will be greater and its heat of combustion smaller than the values calculated for the unperturbed structures. Pauling and his collaborators have demonstrated the existence of mesomerism in a number of compounds by comparison of the experimentally determined heat of formation with that found by summation of the 'bond energies' (deduced from the appropriate thermochemical data).[33] In all cases where mesomerism is to be anticipated, they find that the former is greater than the latter (indicating that the molecule has a smaller energy content). Other criteria are found in the properties of the bonds as determined by electron diffraction and spectroscopic methods (these will be intermediate between those usually associated with single and double

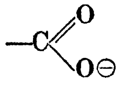
[33] See especially Pauling and Sherman, *J. Chem. Physics*, 1933, 1, 606.

bonds or with double and triple bonds), and the value of the dipole moment of the molecule.[34] In some instances there is also chemical evidence.

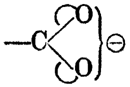
The carbon dioxide molecule provides a simple example. It is linear, and has long been written $O=C=O$ (I). Now if this formula alone represented the molecule, the carbon-oxygen distance should be 1·24 A, but it is actually found to be 1·15 A, an indication that other structures are contributing to the actual state of the molecule. Other possible structures are $\overset{\ominus}{O}—C\equiv\overset{\oplus}{O}$ (II) and $\overset{\oplus}{O}\equiv C—\overset{\ominus}{O}$ (III). The energy of formation of each of these structures can be calculated, at least approximately, and is not far removed from 350,000 calories in each case (II and III are clearly identical). The necessary conditions for mesomerism are thus present; the same molecule can be represented by structures having different arrangements of the electrons but not very different stabilities. The value found for the heat of formation is 380,000 calories, appreciably greater than that calculated for any one of the three structures, and this, together with the interatomic distance, leads to the conclusion that the molecule is represented not by any of the structures which can actually be written, but by a mesomeric state of lower energy. This is conveniently depicted .

The carboxylate ion has a considerable energy of mesomerism. The mesomeric form V, which is reminiscent of the Hantzsch formula, is related symmetrically to the (identical) unperturbed structures IV and VI, the negative charge being distributed equally between the oxygen atoms.

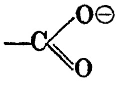
IV



V



VI



Carboxylic acids, esters, and amides show the same effect, but in a lesser degree because the unperturbed forms are not equivalent and the energy of mesomerism is therefore smaller. The ion is thus stabilized to a greater extent than the undissociated acid is, and the acidic character of the carboxyl group (as compared with hydroxyl in an alcohol, for example) may be ascribed to this.[35]

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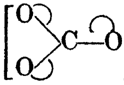
[34] See Chap. IV.

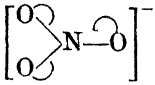
[35] See Pauling, *The Nature of the Chemical Bond.*

Mesomerism in the carbonate and nitrate ions is indicated by the symmetry of these structures as demonstrated by X-ray and infra-red spectroscopy. The three bonds in each case are identical in every respect, and the ions are therefore to be represented as VII and VIII and not as IX and X. In the nitro-group, too, the negative charge is divided equally between the two oxygen atoms as indicated by XI. Many other similar examples might be quoted.[35]

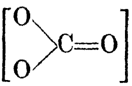
VII



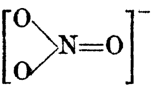
VIII



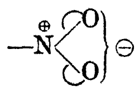
IX



X

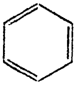


XI

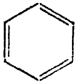


In the case of benzene, the conception of a mesomeric state (XIV) related equally to the two Kekulé structures (XII and XIII) may be regarded as the modernized form of the pre-electronic views of Kekulé and Thiele.

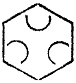
XII



XIII



XIV



In an open-chain compound such as ethylene, the stability of certain of the unperturbed structures (e.g. $>\overset{+}{C}-\overset{-}{C}<$ and $>\overset{-}{C}-\overset{+}{C}<$) is decreased by their dipolar character, and the mesomeric state is relatively near to the non-polar form ($>C=C<$), but a cyclic molecule does not suffer from this limitation and the Kekulé structures are completely equivalent. Accordingly, aromatic compounds have a very considerable energy of mesomerism, to which the peculiar stability of the benzene nucleus is to be ascribed; in the rings of cyclobutadiene and cyclo-octatetraene, however, the angles of 90° and 135° respectively introduce so much strain that the stabilizing effect of resonance is counteracted.[36] In benzene the C—C interatomic distance is 1·39 A, intermediate between that for the C—C single bond (1·54 A) and the C=C double bond (1·34 A), and the molecule is completely symmetrical.[37] The detailed investigation of the benzene problem has shown that, in addition to the two Kekulé structures, the less stable Dewar structures (three in number) make a small contribution, accounting for about 8,000 calories of the total value of 39,000 calories for the energy of mesomerism.[35] Pyridine resembles benzene, and pyrrole, furan, and thiophen have smaller energies of mesomerism in accordance with their more feebly aromatic characters. As would be expected, the energy of mesomerism is higher in polynuclear systems such as naphthalene, anthracene, phenanthrene, quinoline, diphenyl, and indole, and in the combined aromatic-olefinic systems of styrene, stilbene, and *as*-diphenylethylene.

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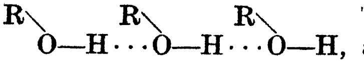
[36] Penney, *Proc. Roy. Soc.* 1934, **146**, A, 223.

[37] Ingold *et al.*, *J. Chem. Soc.* 1936, 912, and following papers; *Proc. Roy. Soc.* 1938, **169**, *A*, 149.

The Hydrogen Bond.[38] The conception of 'co-ordinated' or 'two-covalent' hydrogen, used by Latimer and Rodebush in 1920 to account for molecular association and for the lack of basic strength exhibited by ammonia, is supported both by chemical and by physical evidence. A view of this kind is necessary in order to interpret phenomena such as the existence of acid fluorides with the ion $[F\cdots H—F]^-$, the polymerization of hydrogen fluoride molecules $H—F\cdots H—F$, the association of hydroxylic liquids  $\overset{R\diagdown}{O}—H\cdots\overset{R\diagdown}{O}—H\cdots\overset{R\diagdown}{O}—H$, and the lack of ionization of bases such as $R_3N—H\cdots OH$. X-ray and infra-red spectroscopic observations and dipole moment measurements are in harmony with such an interpretation, and there can be little doubt that atoms are quite frequently joined through hydrogen as indicated above.

The actual nature of the 'linkage' has presented some difficulty, however. It was at first assumed that the hydrogen possessed four shared electrons, but this was shown to be impossible on theoretical grounds. The Pauli Exclusion Principle limits the number of electrons in the first quantum group to two, and hence if the hydrogen had four electrons two would of necessity be in the second quantum group. These would not be bound sufficiently firmly to account for the stability of the hydrogen linkage, however. The difficulty has now been overcome by ascribing the hydrogen bond to resonance between two structures in which the hydrogen is attached to one or the other of the atoms which it joins together, i.e. [X—H Y] and [X H—Y]. As in other cases of mesomerism, it is not supposed that

[38] See Latimer and Rodebush, *J. Amer. Chem. Soc.* 1920, **42**, 1431. G. N. Lewis, *Valence and the Structure of Atoms and Molecules* (New York, 1923), p. 109. Sidgwick, *Electronic Theory of Valency* (Oxford University Press, 1927), pp. 72, 97; *Ann. Reports*, 1933, **30**, 112; 1934, **31**, 40. Huggins, *J. Org. Chem.* 1936, **1**, 407. Pauling, *The Nature of the Chemical Bond.*

oscillation between the two forms occurs, but that the distribution of electrons is intermediate between those represented by them. The energy of the mesomeric state will be smaller than that of either of the unperturbed structures, and hence the hydrogen bond will be stable. Internal hydrogen bond formation in organic molecules is discussed in a later chapter.

II

APPLICATIONS OF THE ELECTRONIC THEORY IN ORGANIC CHEMISTRY. STRENGTHS OF ACIDS AND BASES. THE INDUCTIVE EFFECT

IN 1839 Dumas made the important observation that the substitution of three chlorine atoms in acetic acid led to no change in the fundamental *type* of the compound, and this discovery had a profound influence upon the development of theoretical chemistry.[1] Nevertheless, the replacement of hydrogen by another atom or group frequently results in a very considerable modification of reactivity and chemical characters, and many striking observations of the influences of substituent groups have been recorded. Notable examples are found in the formation of salts by the nitroparaffins, and the exceptional reactivity of certain substituents in the benzene nucleus when one or more nitro-groups are also present. The carbonyl, carbethoxyl, and cyano groups also confer unusual properties upon compounds containing them, as is indicated by the extraordinary mobility of the hydrogen atoms of a methylene group situated between two of these (e.g. formation of metallic derivatives and general reactivity exhibited by β-diketones and by acetoacetic, cyanoacetic, and malonic esters). On the basis of such observations, these groups were designated 'negative'. Of great significance, also, was the discovery of the 'directive influences' of groups in aromatic substitution.[2] It thus became evident that the properties of a bond linking two atoms may be strongly influenced by the nature of other atoms or groups present in the molecule.

A further line of facts was forthcoming from the study of the relative strengths of organic acids and bases, and Ostwald's determination of the dissociation constants of a large number of carboxylic acids[3] provided numerical data upon which comparisons of the characters of substituents could be based. In general, a 'negative' group increased acidity and lowered basicity. Subsequent investigations of substitution reactions, tautomeric changes and other chemical phenomena have thrown further light upon the problem of group influences, while the conception of the dipole moment has made available an additional and powerful method of attack by means of purely physical measurements.[4] In this and succeeding chapters, observations of this type will be considered in the light of the electronic theory of valency.

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[1] See Chap. I. [2] See Chap. III. [3] *Z. physikal. Chem.* 1889, **3**, 418.

Strengths of Organic Acids. The Ionic Theory of Arrhenius appeared in 1887. Strengths of acids had previously been compared by methods involving competition for a limited quantity of a base (Thomsen, 1853; Ostwald, 1878), the catalysed hydrolysis of acetamide, methyl acetate, or cane sugar, or the electrical conductivity at a given concentration (Ostwald). Arrhenius postulated an equilibrium between ions and undissociated molecules, the degree of ionization (α) at any particular concentration (c) being given by the ratio of the equivalent conductivity (Λ) to the conductivity at infinite dilution (Λ_0), and the application of the law of mass action to this equilibrium led to the Ostwald expression (dilution law) for the dissociation constant, viz. $K = \alpha^2c/(1-\alpha)$, or $K = \Lambda^2c/\Lambda_0(\Lambda_0-\Lambda)$. Ostwald determined the dissociation constants of more than two hundred organic acids (all weak electrolytes), values of Λ being derived from the results of conductivity measurements at concentrations ranging from N/4 to N/2048, and Λ_0 being found by an independent measurement on the sodium salt.[5] Ostwald's data have been supplemented by the results of numerous subsequent investigations in which his procedure was employed;[6] these values are now referred to as 'classical' constants, K_{class}.

The failure of the dilution law when applied to strong electrolytes led to various empirical modifications, and ultimately to the theory of Debye and Hückel[7] and its extension by Onsager.[8] This modern view assumes complete dissociation of strong electrolytes, and visualizes the effects upon the measured conductivity of the interionic attractive forces, the frictional resistance of the medium, and the Brownian movement of the ions. The same factors must be considered in weak electrolytes; variations in concentration affect not only the *number* of ions but also, to some extent, their *velocities*, and the values of Λ_0 must be corrected accordingly. Dissociation constants are therefore calculated by the use of the Debye-Hückel-Onsager equation, and the 'true' or 'thermodynamic' constant, K_{therm}, is thus obtained. At the same time, vast improvements in experimental technique have endowed modern determinations with an accuracy not obtainable in Ostwald's day.

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[4] See Chap. IV.

[5] For an account of the theory and technique of conductivity measurements, see Davies, *The Conductivity of Solutions*, 2nd edition (Chapman and Hall, 1933).

[6] e.g. Kendall, *J.C.S.* 1912, **101**, 1275; H. C. Jones *et al.*, *Amer. Chem. J.* 1913, **50**, 1, and references there cited; Walden, *Z. physikal. Chem.* 1892, **10**, 638.

[7] *Physikal. Z.* 1923, **24**, 185, 305.

[8] *Trans. Faraday Soc.* 1927, **23**, 341.

From the standpoint of the organic chemist, the main interest lies in the *relative* values of the dissociation constants of different acids. As a rule, the same general features are observed in the older and the modern data, but for matters of detail, where small differences are considered, it is necessary to rely exclusively upon the accurate values found in recent years. It is still more important to select *comparable* values. Temperature has a definite, though not large, effect upon the dissociation constant; changes of medium naturally exert a very great influence, but as a rule the *order* of strengths is the same in different solvents. The influence of temperature and medium upon dissociation constants calls for further investigation, but there is little reason to doubt that a true comparison of acid strengths can be made by the use of values referring to a single temperature and medium.[9]

A number of accurate values for isolated acids have been obtained during the past few years by the conductometric method.[10] Dissociation constants have also been calculated from the pH values of solutions as determined by electromotive force measurements,[11] and in certain cases by a refinement of the old catalytic method;[12] where comparison is possible, these show good agreement with the values from the more usual conductivity determinations.[13] The thermodynamic dissociation constants of a large number of monocarboxylic acids in water at 25° have recently been determined by Dippy and his co-workers by an expeditious conductometric method;[14] while their procedure does not give the extreme accuracy of 'precision' measurements, the values are doubtless correct within the limits of ±1 per cent., and are strictly comparable. They refer mainly to the benzoic, phenylacetic, β-phenylpropionic, and cinnamic series, and to certain saturated and unsaturated aliphatic acids, and form an important contribution to theoretical organic chemistry.

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[9] This matter has recently been discussed by Dippy in a comprehensive review entitled 'The Dissociation Constants of monocarboxylic acids; their measurement and their significance in theoretical organic chemistry' (*Chem. Reviews*, 1939, **25**, 151). The paper also contains a full account of the influences of substituents upon the strengths of acids, and useful tables of constants. Values quoted in the present work are mainly from these tables.

[10] MacInnes and Shedlovsky, *J. Amer. Chem. Soc.* 1931, **53**, 2419. Saxton *et al.*, ibid. 1933, **55**, 3638; 1934, **56**, 1918; Brockman and Kilpatrick, ibid. 1934, **56**, 1483; Belcher, ibid. 1938, **60**, 2744; Jeffery and Vogel, *J.C.S.* 1932, 2829; 1934, 166; Ives *et al.*, ibid. 1933, 561, 731.

[11] Harned *et al.*, *J. Amer. Chem. Soc.* 1930, **52**, 5079; 1932, **54**, 1350; 1933, **55**, 652, 2379; 1934, **56**, 1042, 2039; Branch and Yabroff, ibid. 1934, **56**, 2568.

[12] Grove, ibid. 1930, **52**, 1404; Deyrup, ibid. 1934, **56**, 60.

[13] For example, 10^5K for acetic acid in water at 25° is found to be 1·747 by conductivity determinations (MacInnes and Shedlovsky, ref. 10), and 1·754 by E.M.F. measurements (Harned and Ehlers, *J. Amer. Chem. Soc.* 1932, **54**, 1350).

The values of the dissociation constants of a number of carboxylic acids, all in water at 25°, are collected in Tables I and II. Table I

TABLE I

Classical Dissociation Constants of substituted Acetic Acids, $X\cdot CH_2\cdot COOH$

X	10^5K	X	10^5K
CH_3	1·34	I	75
H	1·82	Br	138
C_6H_5	5·60	Cl	155
OCH_3	33·50	F	217

Dichloroacetic, 5,140* Trichloroacetic, 121,000*

* The rapid rise of K with the introduction of the second and third chlorine atoms is peculiar; it has recently been discussed by Jenkins (*Nature*, 1940, **145**, 625), who suggests that the ion is stabilized by resonance between a rapidly increasing number of unperturbed structures.

TABLE II

Thermodynamic Dissociation Constants of substituted Aromatic Acids

X	10^5K	
	Benzoic acids $X\cdot C_6H_4\cdot COOH$	*Phenylacetic acids* $X\cdot C_6H_4\cdot CH_2\cdot COOH$
p-OCH_3	3·38	4·36
p-CH_3	4·24	4·27
m-CH_3	5·35	. .
H	6·27	4·88
m-OCH_3	8·17	. .
p-F	7·22	5·68
p-Cl	10·55	6·45
p-Br	10·7	6·49
p-I	. .	6·64
m-F	13·65	. .
m-Cl	14·8	7·24
m-Br	15·4	. .
m-I	14·1	6·93
m-NO_2	32·1	10·8
p-NO_2	37·6	14·1

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[14] See Dippy, ref. 9.

contains 'classical' constants for a series of substituted acetic acids (mainly Ostwald's values), and Table II records thermodynamic constants for benzoic and phenylacetic acids[15] (Dippy *et al.*). In Table III are listed the thermodynamic dissociation constants of some phenylboric acids in 25 per cent. alcohol at 25° (Branch and collaborators[16]).

TABLE III

Thermodynamic Dissociation Constants of substituted Phenylboric Acids, $X \cdot C_6H_4 \cdot B(OH)_2$

X	$10^{10}K$	X	$10^{10}K$
p-OC_2H_5	0·608	p-Br	7·26
p-CH_3	1·00	m-F	11·0
m-CH_3	1·40	m-Cl	13·5
H	1·97	m-Br	14·6
m-OC_2H_5	3·05	m-NO_2	69·0
p-F	3·66	p-NO_2	98·0
p-Cl	6·30		

The values recorded in Tables I to III show that the introduction of a substituent may either increase or decrease the strength of the acid. The magnitude of the influence is dependent, moreover, both upon the nature of the substituent and upon its position. Thus, the dissociation constants of isomeric acids have different values.[17] In a saturated aliphatic acid, the influence of the substituent decreases as its distance from the carboxyl group becomes greater, the fall from the α- to the β-substituted acid being far more pronounced than the subsequent differences; this is illustrated by the following values for chlorinated acids.

TABLE IV

Classical Dissociation Constants of Chloro-Aliphatic Acids

Acid	10^5K
Monochloroacetic	155·0
β-Chloropropionic	8·5
γ-Chlorobutyric	c. 3·0
δ-Chlorovaleric	c. 2·0

Strengths of Bases and Phenols. The strengths of organic bases have been investigated in various ways, the processes employed including the determination of the hydrolysis of their salts by partition,[18] catalytic,[19] conductometric,[20] and solubility methods,[21] electrometric titration,[22] and colorimetric and ultra-violet spectroscopic observations.[23] The measurements are, of course, not of equal value, but the results in general are completely comparable with those already recorded for acids, the strengths being in the reverse order. The relatively scanty data concerning the strengths of phenols[24] are also in general agreement with those referring to acids.

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[15] When calculated from the same conductivity data, the classical constant is a little higher than the thermodynamic constant. Thus, the experimental figures of Dippy and Williams (*J.C.S.* 1934, 1888) for acetic acid give $10^5K_{class} = 1{\cdot}81$, and $10^5K_{therm} = 1{\cdot}76$, while for benzoic acid the values are 6·46 and 6·27.

[16] *J. Amer. Chem. Soc.* 1934, **56**, 937, 1850, 1865.

[17] Only *m*- and *p*-substituted aromatic acids are here referred to; the discussion of *o*-substituted acids is postponed until Chap. XV.

Theoretical Considerations. The wide variations in the dissociation constants of a series of carboxylic acids in a solvent S must be ascribed to the influence of the group R upon the equilibrium[25]

$$\mathrm{R{\cdot}COOH+S \rightleftarrows R{\cdot}COO^{\ominus}+SH^{\oplus}},$$

which becomes, when the solvent is water,

$$\mathrm{R{\cdot}COOH+H_2O \rightleftarrows R{\cdot}COO^{\ominus}+H_3O^{\oplus}}.$$

Those substituents which strengthen the acid favour the right-hand side of the equilibrium, and vice versa. The group may either facilitate or impede the removal of hydrogen ion; at the same time it may operate either against or in favour of recombination.

Flürscheim[26] suggested that there is associated with each group a 'polar factor', which has more recently been defined as 'that effect which, when the substituent occurs at the α-, β-, γ-, or more remote positions in a saturated aliphatic acid, leads consistently to a rise or consistently to a fall in the ionization constant of the acid, and diminishes as the distance from the substituent increases'.[27] The

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[18] Farmer and Warth, *J.C.S.* 1904, **85**, 1713; Flürscheim, ibid. 1909, **95**, 718; 1910, **97**, 84. Moore and Winmill, ibid. 1912, **101**, 1635. Williams and Soper, ibid. 1930, 2469.

[19] Walker, *Z. physikal. Chem.* 1889, **4**, 319; *J.C.S.* 1895, **67**, 576.

[20] Walker, ref. 19; Bredig, *Z. physikal. Chem.* 1894, **13**, 288. Moore and Winmill, ref. 18.

[21] Löwenherz, *Z. physikal. Chem.* 1898, **25**, 385.

[22] Brönsted and Duus, ibid. 1925, **117**, 299; Hall and Sprinkle, *J. Amer. Chem. Soc.* 1932, **54**, 3469; Bennett, Brooks, and Glasstone, *J.C.S.* 1935, 1821; Davies and Addis, ibid. 1937, 1622; Davies, ibid. 1938, 1865.

[23] Hammett *et al.*, *J. Amer. Chem. Soc.* 1932, **54**, 2721; 1934, **56**, 2010; 1935, **57**, 2103.

[24] e.g. Bader, *Z. physikal. Chem.* 1890, **6**, 289; Walker, ibid. 1900, **32**, 137; Hantzsch and Farmer, *Ber.* 1899, **32**, 3066; Walker and Cormack, *J.C.S.* 1900, **77**, 18; Boyd, ibid. 1915, **107**, 1538.

[25] The solvation of the hydrogen ion in solution, postulated by Fitzgerald and Lapworth (*J.C.S.* 1908, **93**, 2163, 2187), is now well established; see Taylor, *A Treatise on Physical Chemistry*, 2nd edition (Macmillan, 1931), vol. i.

[26] *J.C.S.* 1909, **95**, 718.

[27] Cocker, Lapworth, and Walton, ibid. 1930, 443.

'polar factor' is equivalent to the conception of 'positivity' or 'negativity' which Derick, on the basis of the equation $A = RT \log K$ for the change in free energy of ionization, proposed to express quantitatively by a logarithmic function of the dissociation constant of the appropriate substituted monocarboxylic acid.[28] Derick also pointed out that the effect may be transmitted to the carboxyl group either through the intervening atoms in the molecule or directly through the medium.

The polar factor associated with a substituent will, of course, modify the strength of a base in the reverse direction. The equilibrium here is

$$\mathrm{B+S \rightleftarrows BH^{\oplus}+(S{-}H)^{\ominus}}$$

or, for water as solvent,

$$\mathrm{B+H{\cdot}OH \rightleftarrows BH^{\oplus}+OH^{\ominus}},$$

and influences which facilitate the removal of hydrogen ion from an acid will oppose the co-ordination of proton with the base, and vice versa.

The electronic interpretation of the polar factor was given by G. N. Lewis, in terms of an unequal sharing of the electron-pair forming a covalent bond.

> 'The pair of electrons which constitutes the bond may lie between two atomic centres in such a position that there is no electric polarization, or it may be shifted toward one or the other atom in order to give to that atom a negative, and consequently to the other atom a positive charge. . . .
>
> 'Let us consider once for all that by a negative element or radical we mean one which tends to draw toward itself the electron pairs which constitute the outer shells of all neighbouring atoms, and that an electropositive group is one that attracts to a less extent, or repels, these electrons. . . .
>
> 'As a familiar example we may consider acetic acid in which one hydrogen is replaced by chlorine, $H_2ClCCOOH$. The electrons, being drawn towards the chlorine, permit the pair of electrons joining the methyl and carboxyl groups to approach nearer to the methyl carbon. This pair of electrons, exercising therefore a smaller repulsion upon the other electrons of the hydroxyl oxygen, permit these also to shift in the same direction. In other words, all the electrons move towards the left, producing a greater separation of the electrons from the hydrogen of the hydroxyl, and thus a stronger acid. This simple explanation is applicable to a vast number of individual cases. It need only be borne in mind that although the effect of such a displacement of electrons at one end of a chain proceeds through-

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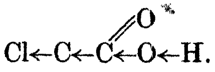
[28] *J. Amer. Chem. Soc.* 1911, **33**, 1152.

out the whole chain, it becomes less marked the greater the distance and the more rigid the constraints which hold the electrons in the intervening atoms.'[29]

These displacements are commonly represented  $Cl \leftarrow C \leftarrow \overset{O}{C} \leftarrow O \leftarrow H$. Regarding the transmission of the effect, Lewis writes:

> 'It is not at all certain that the whole effect is produced through the carbon chain. If we knew how to construct thoroughly satisfactory spatial models of our molecules, we might see how in certain cases there might be some more immediate steric effect which would exaggerate the effect produced through the chain. But that the latter effect, passing through the molecule atom by atom, is a real one we have no reason to doubt.'[30]

On this view, which is now accepted universally, increased acidity arises from the electron-attractive nature of the substituent, while an enhanced basic (or decreased acidic) character is to be ascribed to electron-repulsion, the effect being transmitted both through the intervening bonds and through the medium. The term 'Inductive Effect', due to Ingold,[31] is now employed in place of Flürscheim's expression 'Polar Factor'. Hydrogen is the natural standard of reference, and a group which, relatively to hydrogen, repels electrons, is spoken of as having a +I effect, while the influence of a group which is relatively electron-attractive is designated —I.[32] It has been suggested that those portions of the effect which are transmitted through the chain and through space respectively might be distinguished by the terms 'inductive' and 'direct';[33] since, however, there is no means of separating them quantitatively, the term 'Inductive Effect' is invariably used to denote the sum of the two.

The values of the dissociation constants of the substituted acetic acids recorded in Table I indicate that methyl is electron-repulsive

[29] *J. Amer. Chem. Soc.* 1916, **38**, 781; *Valence and the Structure of Atoms and Molecules* (Chemical Catalog Co., New York, 1923), pp. 83, 84.

[30] *Valence*, p. 139.

[31] *Ann. Reports*, 1926, **23**, 140. Compare *Rec. trav. chim.* 1929, **48**, 797; *Chem. Reviews*, 1934, **15**, 225. The term 'general polar effect' has also been used frequently (e.g. Allan, Oxford, Robinson and Smith, *J.C.S.* 1926, 401).

[32] Sir Robert Robinson [*J.* 1932, 1445; *Outline of an Electrochemical Theory of the Course of Organic Reactions* (Institute of Chemistry, 1932), p. 34] has suggested that these signs should be reversed, in accordance with the charge conferred by the group upon adjacent atoms. The original signs are more commonly used, however, and will be employed throughout this book. Their correspondence with the signs normally written for dipole moments (Chap. IV) is convenient.

[33] Ingold and Vass, *J.C.S.* 1928, 417.

(+I) in character while the remaining groups are electron-attractive (—I) in the following order:

Decreasing electron attraction ⟶

$$\underbrace{F > Cl > Br > I > OCH_3 > C_6H_5}_{-I} > H > \underbrace{CH_3}_{+I}.$$

The dissociation constants for *m*- and *p*-substituted aromatic acids lead similarly to the sequence

$$NO_2 > \text{Halogen} > H > CH_3$$

for decreasing electron-attractive character, and this order of groups appears in the data referring to a very large number of chemical processes. A more detailed inspection of the values of the dissociation constants, however, reveals certain peculiarities when the substituent is linked to the benzene nucleus. The following are the most obvious:

1. Whereas methoxyl increases the dissociation constant of acetic acid, and also of benzoic acid when it is in the *m*-position, *p*-methoxyl has the reverse effect; it weakens both benzoic and phenylacetic acids. *p*-Ethoxyl has the same influence upon the strength of phenylboric acid and, indeed, the peculiarity is general for —OR groups.

2. The nitro-benzoic and -phenylacetic acids are much stronger than the corresponding unsubstituted acids; the effect of *p*-NO_2, however, is more powerful than that of *m*-NO_2, in spite of the greater distance of the substituent from the carboxyl group.

3. Halogens cause an increase of strength in both aliphatic and aromatic acids, and in the latter their effect is greater in the *m*-position than in the *p*-position, as would be expected. The order of strengths of the halogenoaromatic acids *among themselves* is not, however, that found in the halogenoacetic acids, viz. $F > Cl > Br > I$; in the *p*-halogenoaromatic acids this order is completely inverted, while there is a partial inversion in the *m*-substituted acids (the strengths of which do not, however, differ very greatly). Similar irregularities are observed in the strengths of the halogen-substituted anilines and phenols recently determined by Bennett, Brooks, and Glasstone,[34] and recorded in Table V.

These peculiarities lead to the conclusion that, while the relative strengths of the saturated aliphatic acids are governed by the Inductive Effects of the substituent groups and may be regarded as a measure of the magnitudes of these effects, an additional factor

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[34] *J.C.S.* 1935, 1821.

TABLE V

Strengths of Anilines and Phenols in 30 per cent. alcohol at 25°

X	$10^{12}K_b$		$10^{10}K_a$	
	p-X·C_6H_4·NH_2	m-X·C_6H_4·NH_2	p-X·C_6H_4·OH	m-X·C_6H_4·OH
H . .	126		0·32	
F . .	120	10·5	0·26	1·51
Cl . .	28·8	8·51	1·32	4·90
Br . .	21·9	7·94	1·55	4·37
I . .	15·1	7·59	2·19	3·89

operates when the substituent is attached to the aromatic nucleus. The influence of an atom or group cannot be expressed completely in terms of its Inductive Effect, for other influences are encountered when the group is linked to a suitable system. The existence of these additional influences will be exemplified further in the sequel, and their origin and nature will be discussed in Chapter VI.

III

APPLICATIONS OF THE ELECTRONIC THEORY IN ORGANIC CHEMISTRY. SUBSTITUTION IN AROMATIC COMPOUNDS

THE term 'substitution', when used in its widest sense, refers to all processes which lead to the replacement of *any* atom or group by *any other*, as represented by the substitution of Z for X in the reactions (*a*) and (*b*) below:

$$RX+YZ = RZ+XY \qquad (a)$$

$$RX+Z = RZ+X. \qquad (b)$$

Reaction (*a*) is a substitution in a 'four-centre system' and involves the rupture of two bonds; reaction (*b*) occurs in a 'three-centre system' and only one bond is ruptured.

The familiar replacement of hydrogen, $RH+YZ = RZ+HY$ (as in $CH_4+Cl_2 = CH_3Cl+HCl$, or $C_6H_6+NO_2OH = C_6H_5NO_2+H_2O$), first investigated by Dumas over a century ago, is in reality a particular example of the more general phenomenon. It will be convenient, however, to adhere for the present to long-established convention, and to use the word 'substitution' to denote this special case. The contrast between the substitution reactions of the paraffins and the addition processes to which the olefins are susceptible forms the main justification for classifying these hydrocarbons as saturated and unsaturated respectively, while the predominance of substitution in aromatic compounds has played a leading part in connexion with the problem of the structure of benzene. Observations of nuclear substitutions in benzene derivatives form one of the foundation stones of the modern electronic theory of the reactions of organic compounds, and a survey of the main features of these processes will be given here. Processes of replacement in their wider aspect are considered in a later chapter.

Kekulé's ring formula for benzene was published in 1865.[1] It has been confirmed of recent years by X-ray evidence, and, in fact, the Kekulé model of a nucleus with alternate single and double bonds still remains the most convenient representation of aromatic compounds, for the two Kekule structures are the main participants in the mesomeric state.[2] By 1874 the problem of the orientation of benzene derivatives was solved, largely through the work of Körner. Then, at an early date, it became evident that the introduction of a further group into a nucleus already containing one or more substituents did not lead to the production of all the possible isomerides in equal quantities. The main factor determining the position of substitution was the nature of the group or groups already present; thus, hydroxyl, alkoxyl, amino, dialkylamino, halogens, and alkyl groups directed the entering group mainly or entirely to the positions *ortho* and *para* to themselves, while the nitro, carbonyl, carboxyl, and sulphonic acid groups caused the new substituent to take up principally the *meta*-position. Attempts to express these facts in a generalized form led to various orientation rules, of which the best known were those of Körner (1874), Hübner (1875), Nölting (1876), Armstrong (1887), Crum Brown and Gibson (1897), and Vorländer (1902). In these generalizations a connexion was sought between orientation and other characters of the directing group X, such as its acidic nature (Körner, Hübner, Nölting), the valencies of its atoms (Armstrong), its relationship with the compounds XH or XOH as indicated by the capacity for direct oxidation possessed by XH (Crum Brown and Gibson), and its saturated or unsaturated nature (Vorländer). None of these rules, however, embraced the whole of the experimental observations.

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[1] For an excellent account of the early work on the benzene problem see Lachman, *The Spirit of Organic Chemistry* (New York, 1899), Chap. III.

In 1895 Holleman proceeded to a systematic and quantitative study of the problem of aromatic substitution.[3] He devised improved methods of separating and estimating the isomerides, and was able to show that, when a second group enters a nucleus already containing one substituent, all three derivatives are usually formed, though in very unequal proportions. Pure *op*- or pure *m*-substitution is rare, if it ever occurs, but the entering group takes up *principally* the *m*- or the *o*- and *p*-positions with respect to the substituent already present. The entry of the second substituent, in fact, takes place by three simultaneous reactions. They have widely differing velocities, however, and one or more may sometimes be so slow as to give hardly perceptible amounts of the corresponding isomerides.

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[2] See Chap. I, p. 21.

[3] *Die direkte Einführung von Substituenten in den Benzolkern* (Leipzig, 1910). The most widely applicable method of determining the proportions of isomerides consists in the study of fusion curves.

Thus, only the *m*-derivative has been detected in the products of substitution of phenyltrimethylammonium salts and other 'onium' compounds where the directive group is associated with an integral positive charge;[4] substitution in phenols and phenolic ethers has usually been regarded as occurring exclusively at the *o*- and *p*-positions,[5] but small quantities of *m*-isomerides have more recently been detected in the nitration products.[6] It is probably correct to state that, in certain limiting cases, the quantities of one or more isomerides are too small for experimental detection, while there are other instances where the very small proportions of certain isomerides render their detection difficult though not impossible.

Holleman further showed that, while other factors such as the nature of the attacking reagent, temperature, and catalysts affect the proportions of the isomerides, sometimes to a very appreciable extent, the directive influence of the substituent is of prime importance; a given group directs either *op* or *m*, independently of external conditions. This is known as the Law of Conservation of Substitution Type. Certain apparent exceptions admit of a simple explanation; perhaps the most obvious is the production of nearly 50 per cent. of *m*-derivative when aniline is nitrated in presence of concentrated sulphuric acid,[7] a result which is due to salt-formation with the consequent change of the directing group from $—NH_2$ to $—NH_3^{\oplus}$. The considerable variations in the relative quantities of the *o*- and *p*-isomerides which frequently accompany a change in the substituting reagent are, of course, 'within the type', whatever be their explanation. It must be pointed out, however, that there is really no sharp boundary line between *op*- and *m*-directive groups, but a gradual transition. This is illustrated by the steady variation in the percentage of *m*-isomeride in the products of nitration of the side-chain chlorinated derivatives of toluene ($C_6H_5 \cdot CH_3$, 4 per cent.; $C_6H_5 \cdot CH_2Cl$, 12 per cent.; $C_6H_5 \cdot CHCl_2$, 33 per cent.; $C_6H_5 \cdot CCl_3$, 48 per cent.[8]). The *relative* directive powers of different groups were deduced by Holleman from determinations of the proportions of the isomerides formed when a third substituent enters a nucleus already containing the two groups to be compared. Thus, in the nitration of *p*-chlorotoluene the isomeride having the nitro-group *ortho* to chlorine was in excess of that with this group *ortho* to methyl, and he concluded that the directive influence of chlorine was the greater. By experiments of this type he arrived at the following sequences:

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[4] For references see *Ann. Reports*, 1926, **23**, 130.

[5] Holleman, op. cit. (ref. 3), p. 155.

[6] Arnall, *J.C.S.* 1924, **125**, 811; Griffiths, Walkey, and Watson, ibid. 1934, 631.

[7] Holleman, Hartogs, and van der Linden, *Ber.* 1911, **44**, 704.

[8] Flürscheim and Holmes, *J.C.S.* 1928, 1611. Compare Holleman, Vermeulen, and de Mooy, *Rec. trav. chim.* 1914, **33**, 1.

op-directive influence $OH > NH_2 >$ Halogen $> CH_3$
m-directive influence $COOH > SO_3H > NO_2$.

Holleman pointed out the very important fact that *op*-substitution is normally far more rapid than *m*-substitution. This is obvious, indeed, in elementary laboratory work; for example, the practically instantaneous bromination of aniline and phenol to give the *s*-tribromo-derivatives offers a sharp contrast with the slow *m*-nitration of nitrobenzene which reacts far less readily than does benzene itself. In naphthalene and anthraquinone, moreover, the presence of an *op*-directive group normally leads to further substitution in the same nucleus, while a *m*-directive group causes substitution to occur in the other ring. The inevitable conclusion is that, in general, *op*-substitution is associated with activation, and *m*-substitution with deactivation of the benzene nucleus. The significance of this was appreciated by Holleman. Kekulé regarded substitution as preceded by addition of the reagent molecule, and Holleman suggested that *op*-directive influence arises from the facilitation of addition at the 1.2 and 1.4 positions (Kekulé's benzene formula), while *m*-substitution is the result of the retardation of this addition.[9]

A quantitative study of the effects of certain groups upon the reactivities of the different positions in the aromatic nucleus has recently been carried out by Ingold and his collaborators.[10] Relative speeds of nitration were determined by competition experiments in which benzene and one of its derivatives C_6H_5X were nitrated together, using much less than the quantity of nitric acid required to react completely with both. The relative quantities of the nitro-derivatives $XC_6H_4NO_2$ and $C_6H_5NO_2$ in the product were then a measure of the relative speeds of nitration of C_6H_5X and benzene. The figures so obtained were combined with the percentages of *o*-, *m*-, and *p*-nitro-derivatives formed in the nitration of C_6H_5X, and thus the reactivities of the various positions in C_6H_5X relative to the reactivity of one of the positions in unsubstituted benzene were calculated. The results of this work are summarized in the table below.

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[9] *Chem. Reviews*, 1924, **1**, 187.

[10] *J.C.S.* 1927, 2918; 1931, 1959; 1938, 905, 918.

Compound	*Relative Reactivities*		
	o	*m*	*p*
C_6H_6	1	1	1
$C_6H_5\cdot CH_3$	43	3	55
$C_6H_5\cdot COOC_2H_5$	0·0026	0·0079	0·0009
$C_6H_5\cdot Cl$	0·030	0·000	0·139
$C_6H_5\cdot Br$	0·037	0·000	0·106

It is evident from these figures that —CH_3, a typical *op*-directive group, activates the whole nucleus to some extent, but especially the *o*- and *p*-positions. On the other hand, the ester grouping —$COOC_2H_5$, a *m*-directive group, lowers the reactivities of all positions below that of unsubstituted benzene, but it deactivates the *o*- and *p*-positions to a greater degree than the *m*-position, thus leading to *m*-substitution. Directive influences are therefore to be ascribed to the selective activation or deactivation of the *o*- and *p*-positions.

The most powerful of all directive groups are those carrying an integral charge; thus, a positively charged group such as —$\overset{+}{N}(CH_3)_3$ directs exclusively *meta* so far as can be ascertained, while negatively charged oxygen has a much greater influence than hydroxyl or alkoxyl, as shown by the fact that the phenoxide ion is halogenated far more readily than undissociated phenol or a phenolic ether.[11] These facts connect *op*-substitution and nuclear activation with a *repulsion* of electrons by the directing group, and *m*-substitution and nuclear deactivation with *attraction* of electrons. A superficial consideration of the process of substitution would, indeed, lead to a similar conclusion. Considering, as an example, nuclear chlorination, $RH + Cl{-}Cl = RCl + H{-}Cl$, it is evident that the chlorine atom which forms chloride ion must retain the covalent pair of the chlorine molecule, and the atom which enters the nucleus will therefore seek a point where there are electrons available for the completion of its octet. Thus, the chlorine molecule is an electron-seeking or 'electrophilic' reagent,[12] and the same applies to the other common substituting agents such as nitric and sulphuric acids. The reactive points of the aromatic nucleus will therefore be those of highest electron availability, and the conclusion is reached that *op*-substitution is the result of the accession of electrons to the nuclear carbon atoms situated *o* and *p* with respect to an electron-repulsive group, while *m*-substitution takes place when an electron-attractive group withdraws electrons from the nucleus as a whole, but especially from the *o*- and *p*-positions.

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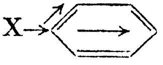
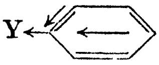
[11] Soper and Smith, *J.C.S.* 1926, 1582; 1927, 2757.

[12] The classification of reagents is considered more fully in Chap. X.

op-substitution.



m-substitution.



Clearly, if the influence of a substituent were due solely to its inductive effect, all those groups which increase the strength of a saturated aliphatic acid would lead to *m*-substitution; the *op*-directive influence of groups such as hydroxyl and halogens thus confirms the conclusion, already reached on different grounds,[13] that these groups give rise to electronic displacements which are distinct from their inductive effects. The case of halogens is particularly complex. In accordance with their electron-attractive characters, they deactivate the nucleus (see table on previous page), and a halogen atom in one ring of naphthalene causes a second substituent to enter the other ring. Yet their directive influence is *op*. These peculiarities are discussed in Chapter VI.

Substituent groups in a saturated side-chain (e.g. X in $C_6H_5 \cdot CH_2X$) exert influences in accordance with their inductive effects. This is illustrated by the increasing percentage of *m*-derivative present in the products of nitration in the following instances:

$C_6H_5 \cdot CH_3$	$C_6H_5 \cdot CH_2Br$	$C_6H_5 \cdot CH_2Cl$	$C_6H_5 \cdot CH_2F$	$C_6H_5 \cdot CH_2 \cdot NO_2$
4 per cent.	7 per cent.	12 per cent.	18 per cent.	67 per cent.

(compare also the chlorinated derivatives of toluene referred to on p. 36). The falling off of the effect with increasing distance of the group from the nucleus is exemplified in the following series of figures for the percentage of *m*-derivative formed on nitration:

$C_6H_5 \cdot \overset{+}{N}(CH_3)_3$	$C_6H_5 \cdot CH_2 \cdot \overset{+}{N}(CH_3)_3$	$C_6H_5 \cdot CH_2 \cdot CH_2 \cdot \overset{+}{N}(CH_3)_3$	$C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot \overset{+}{N}(CH_3)_3$
100 per cent.	88 per cent.	19 per cent.	5 per cent.

$C_6H_5 \cdot NO_2$	$C_6H_5 \cdot CH_2 \cdot NO_2$	$C_6H_5 \cdot CH_2 \cdot CH_2 \cdot NO_2$
93 per cent.	67 per cent.	13 per cent.

[13] See Chap. II.

Before concluding this survey of the facts relating to aromatic substitution, a brief reference must be made to two recent generalizations or orientation rules which appear to be of general application. Hammick and Illingworth[14] have pointed out that in a benzene derivative C_6H_5XY, when Y is in a higher periodic group than X, or, if in the same group, is of lower atomic weight, XY is *m*-directive; in all other cases, including that where the substituent is a single atom, *op*-direction results. The rule appears to hold generally, with the reservation that an integral charge residing on XY will always take control, a positive charge directing *m*, and a negative charge *op*. The other observation is due to Sutton, who has detected a relationship between the directive influence of a group X and the sign of the difference between the moments of Aryl X and Alphyl X.[15] This is dealt with later (Chap. IV).

It is interesting to note that the replacement of nuclear hydrogen by its heavy isotope deuterium is subject to the same rules which govern other substitutions.[16] Thus, phenol and aniline are 'deuterated' exclusively at the *o*- and *p*-positions, and substituents already present accelerate or retard the process in the usual way [e.g. O^-, $N(CH_3)_2$, and OCH_3 lead to more rapid deuteration and SO_3H reduces the speed].

Side-Chain Reactions. Reference has been made to the 'electrophilic' character of the common reagents which bring about the replacement of nuclear hydrogen by another atom or group. They attack those points of the molecule where electrons are available, and substitution is therefore, in general, accelerated by *op*-directive groups, which give rise to such points. Olivier was the first to direct attention to the existence of a 'correspondence' between the effects of groups upon nuclear substitution of hydrogen and upon certain reactions in a side-chain.[17] He studied the hydrolysis of a series of substituted benzyl chlorides in aqueous alcohol (solution originally neutral and becoming acid),[18]

$$X \cdot C_6H_4 \cdot CH_2Cl + H \cdot OH = X \cdot C_6H_4 \cdot CH_2OH + HCl.$$

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[14] *J.C.S.* 1930, 2358.

[15] *Proc. Roy. Soc.* 1931, **133 A**, 668.

[16] Ingold, Raisin and Wilson, *J.C.S.* 1936, 1637; Best and Wilson, ibid. 1938, 28.

[17] *Rec. trav. chim.* 1923, **42**, 775.

[18] Bennett and B. Jones (*J.C.S.* 1935, 1815) have more recently studied the same reaction, with similar results.

The order of decreasing reactivity when X varied was

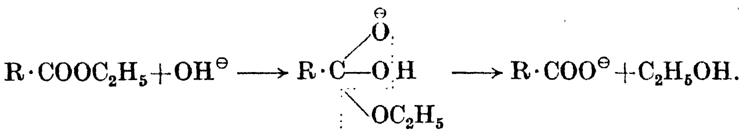
$$CH_3 > H > Hal > NO_2;$$

i.e. groups which increase the speed of nuclear substitution of hydrogen also increase that of the replacement of chlorine in the side-chain, and vice versa. A number of other side-chain processes are accelerated by electron-repulsive groups and retarded by electron-attractive groups in the nucleus, and all of these are referred to as reactions of 'Type A'.[19] They obviously include processes in which an electrophilic reagent brings about the substitution of hydrogen as in side-chain chlorination, and the formation of quaternary ammonium salts from dialkylanilines where the controlling factor is the electron-availability of the nitrogen atom.[20]

There exists also a large class of side-chain reactions, termed 'Type B', in which substituents have the reverse effect; the general order of velocities is indicated by the sequence

$$NO_2 > Hal > H > CH_3.$$

These include various *alkaline* hydrolyses, in which the controlling step is the attack of the hydroxyl ion; e.g. the hydrolysis of benzoic, phenylacetic, and cinnamic esters[21] which may be formulated



$$R\cdot COOC_2H_5 + OH^{\ominus} \longrightarrow R\cdot \overset{\overset{\ominus}{O}}{\underset{OC_2H_5}{C}}—OH \longrightarrow R\cdot COO^{\ominus} + C_2H_5OH.$$

Hydroxyl, in common with other anions, has its full quota of electrons, and hence seeks a point of attack where there is a *deficiency* of electrons; it is positive-centre-seeking or 'nucleophilic'.[22] Alkaline hydrolyses are therefore favoured by electron-attractive substituents, which tend to draw electrons away from the side-chain. The alkaline hydrolysis of benzyl chlorides is a reaction of 'Type B'.[23] Their hydrolysis in acid solution is of 'Type A' (see above) because it is not a straightforward bimolecular reaction; its speed is governed mainly by the removal of the chloride ion. Substitutions of this type are considered fully later (Chap. X).

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[19] Ingold and Rothstein, *J.C.S.* 1928, 1217. See list of reactions given by Williams, ibid. 1930, 40.

[20] See Davies and Lewis, ibid. 1934, 1599.

[21] Kindler, *Annalen*, 1926, **450**, 1; 1927, **452**, 90; 1928, **464**, 278.

[22] See further Chap. X.

[23] Shoesmith and Slater, *J.C.S.* 1924, **125**, 1312, 2278.

IV

THE NEW PHYSICAL METHODS OF INVESTIGATION

THE recent advances in theoretical organic chemistry have been greatly assisted, and to a large extent, indeed, made possible, by the development of a number of purely physical methods of investigation. The knowledge thus gained regarding the dimensions and other properties of the bonds by which atoms are linked has been applied to the solution of many problems relating to structure, reactivity, and stereochemical configuration. A brief account of some of these new physical methods is given in this chapter.

1. *X-Ray Methods*[1]

X-rays were discovered by Röntgen in 1895, and examination of their behaviour showed that, while in many respects they resembled visible light, there were nevertheless marked differences between the two types of radiation. In particular, X-rays were not diffracted by the ordinary gratings; this was due to the fact that their wave-length (of the order 10^{-7} to 10^{-9} cm. as compared with 10^{-5} cm. for visible light) was much shorter than the distances between the lines of any grating that could be constructed. In 1912, however, Laue suggested that a crystal might be employed for the purpose, and the correctness of this suggestion was demonstrated experimentally by Friedrich and Knipping. The distances between the parallel planes of which the crystal is composed are of the same order of magnitude as the wave-length of X-rays, and this made possible their diffraction. Friedrich and Knipping passed a beam of the radiation through a crystal of zinc blende in a direction parallel to one of the axes of symmetry, and a photographic plate exposed to the emergent beam bore a symmetrical distribution of spots. They had thus obtained an X-ray spectrum for the first time, since each spot represented a ray of a particular wave-length. The classic investigations of Sir W. H. Bragg and his son, W. L. Bragg, followed. In their X-ray spectrometer the crystal was used as a *reflection* grating, and the resulting spectra were much easier to interpret than those of the 'Laue photographs'. When a beam of monochromatic X-radiation of wave-length λ impinges on a crystal at an angle of incidence θ, some of the rays are reflected from the surface, and others from the planes in the interior. The resultant beam is the sum of all these. Fig. 2 illustrates the routes of rays which leave the crystal along the same path, and it is evident that such rays will either reinforce or destroy one another. From the geometry of the figure it can be shown very simply that reinforcement will occur if the angle of incidence is given by the expression $n\lambda = 2d \sin \theta$, where d is the distance between successive planes of the crystal, and n is a whole number. The reflected beam is of appreciable intensity only for these particular values of θ, and therefore, by measuring the angles of incidence at which such a beam is obtained, a relationship between λ and d is found. These angles were determined by passing the reflected beam into an ionization chamber (containing an easily ionizable gas such as sulphur dioxide) and observing an electroscope into which the ions of one sign were driven by an electric field.

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[1] See Sir W. H. and W. L. Bragg, *The Crystalline State* (G. Bell & Sons, 1933). Recent work is summarized in the 'Crystallography' section of the *Annual Reports* for 1933 and subsequent years.

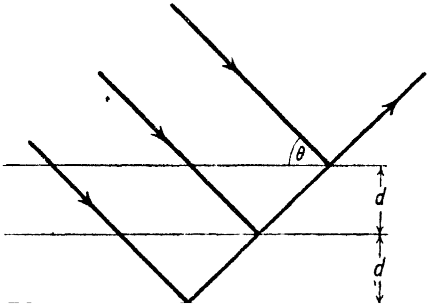

FIG. 2.

The structures of a large number of crystals have been elucidated in this way, and interatomic distances calculated. A similar procedure (in which, however, the spectra were photographed) was employed by Moseley in his determination of atomic numbers from the wave-lengths of the characteristic X-rays of various elements.[2] These rays are produced when the element (or a compound containing it) is subjected to bombardment by fast-moving electrons (cathode rays); by using a crystal for which the constant d was known, Moseley was able to measure their wave-lengths, which were found to bear a simple relation to the atomic numbers. The application of Moseley's method of X-ray analysis has resulted in the discovery of at least four of the six elements which were then missing.

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[2] *Phil. Mag.* 1913, **26**, 1024; 1914, **27**, 703.

The original Bragg method required fairly large, well-formed crystals, but it has since been extended by Debye and others in such a way as to make it applicable to crystalline powders, and even to liquids and gases. The results obtained with liquids are very difficult to interpret, but the wide separation of the molecules in a gas rendered the method of X-ray scattering by gases a very promising one. The scattering power of the relatively small amount of matter in a given volume of a gas is very weak, however, and long exposures are necessary, amounting to several hours at ordinary pressure. For this reason the analogous process of electron diffraction has proved much simpler and more useful (see section 3 of this chapter).

From the chemical point of view, the most significant results of the earlier X-ray work were the following: (1) the observed contrast between salts where only the individual ions were detected and covalent compounds in which the whole molecules were discernible; (2) the confirmation of the tetrahedral arrangement of the valencies of carbon from the structure of diamond; and (3) the demonstration of the actual existence of a hexagon of carbon atoms in aromatic compounds. More recent applications to the problems of organic chemistry include Mrs. Lonsdale's demonstration of the uniplanar (flat) character of the aromatic nucleus in hexamethyl- and hexachloro-benzenes,[3] and numerous instances of the use of X-ray methods in the determination of chemical structure, as exemplified by Bernal's contribution to the problem of the ring system of the sterols and allied compounds (cholane group).[4] The configurations of the valencies of a number of elements other than carbon have also been determined by X-ray examination.[5]

2. *Visible and Infra-red Spectra*[6]

The study of absorption spectra in the visible and infra-red regions has become, of recent years, a valuable source of information. Apart from variations in kinetic energy of translation, the only energy changes which an *atom* can undergo are due to the movement of one or more electrons into other levels. The energy is purely *electronic*, and the spectra to which the transitions give rise consist of series of lines (which, however, have a fine structure owing to the subsidiary levels, see Chap. I). The case of a molecule is more complex, however. Electronic transitions can occur here also, and the frequency of the resulting radiation is governed by the expression $h\nu = E_e - E'_e$, the quantum being of such magnitude that the spectrum is in the visible or ultra-violet region. Changes in *electronic* energy, however, are always accompanied by changes in *vibrational* and *rotational* energy. Taking the simplest case, namely, that of a diatomic molecule, there are variations both in the amplitude of oscillation of the nuclei in the line joining their centres, and in the frequency of rotation of the whole molecule about an axis perpendicular to this line; these changes are, of course, responsible for the well-known difference in the ratio of the specific heats of monatomic and diatomic gases. The total energy of the molecule, excluding kinetic energy, is therefore given by the expression

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[3] *Proc. Roy. Soc.* 1929, **123**, A, 494; 1931, **133**, A, 536.

[4] See *Ann. Reports*, 1933, **30**, 423, and references there cited.

[5] See Chap. XVI.

[6] For a fuller account see Glasstone, *Recent Advances in Physical Chemistry*, 3rd edition (Churchill, 1936); also, Barratt, *Ann. Reports*, 1926, **23**, 304. The results of spectroscopic measurements are discussed by Sidgwick in *The Covalent Link in Chemistry* (Cornell University Press, New York, 1933); see also Sidgwick and Bowen, *Ann. Reports*, 1931, **28**, 367. References to original papers and larger treatises may be found in the above.

$$E = E_e + E_v + E_r,$$

and the complete energy change involved when an electronic transition occurs is

$$h\nu = (E_e - E'_e) + (E_v - E'_v) + (E_r - E'_r).$$

The vibrational quanta are smaller (by a factor of 0·1 to 0·01) than electronic quanta, and rotational quanta are much smaller still (about 0·01 of vibrational). The spectra produced by changes in the electronic energy levels are therefore series of bands, each band consisting of lines so closely spaced as to appear continuous except when observed with an instrument of high resolving power. Each line in the band represents a change in vibrational energy, and has a fine structure due to rotational changes.

The energy levels of a molecule are shown diagrammatically in Fig. 3. The lines in I represent different electronic states; for each of these there are a number of vibrational levels shown by the thinner lines in II; the dotted lines in III represent the rotational states associated with each vibrational level. The general form of an electronic band spectrum will be clear from an inspection of Fig. 4, in which the bands due to electronic transitions are seen to consist of lines indicating changes in vibrational energy, each line having a fine structure on account of accompanying rotational changes.[7]

Studies of electronic band spectra have led to the discovery of isotopes of oxygen, carbon, and nitrogen, which are present in proportions too small for detection by the mass spectrograph, and also to the observation of two forms of the hydrogen molecule, called *ortho-* and *para*-hydrogen, in which the nuclei have respectively the same and opposite directions of spin. Owing to the complexity of electronic band spectra, however, and the consequent difficulty of interpretation, the examination of vibration-rotation spectra is usually preferred. The vibrational quantum is of such small magni-

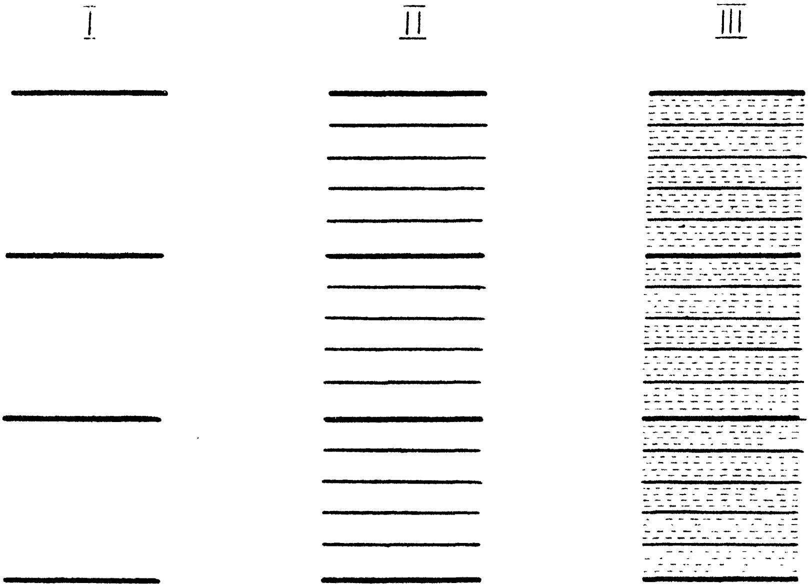

FIG. 3.

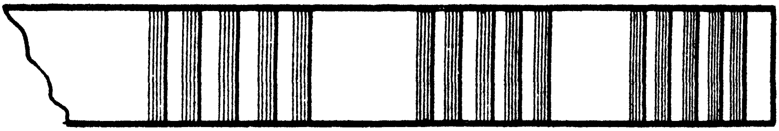

FIG. 4.

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[7] Diagrams of this type are given by Allmand, *The Nature of Simple Molecules and of Elementary Processes* (Institute of Chemistry, 1932).

tude that these spectra, which arise from changes in vibrational energy with accompanying rotational changes, are in the near infra-red. The energy change is now

$$h\nu = (E_v - E'_v) + (E_r - E'_r),$$

and, in a diatomic molecule, for each vibrational change the spectrum consists of two series of lines (*P* and *R* branches), one on either side of a central line (*Q* branch, not observed) having the fundamental frequency of vibration of the molecule. The moment of inertia of the molecule, and hence the distance apart of the nuclei, can thus be determined. The same quantities have also been found, in some cases, from pure rotation spectra in the far infra-red. These are the least complicated of all molecular spectra, and for a diatomic molecule the moment of inertia I is got from the simple formula

$$\nu = nh/4\pi^2 I,$$

where n is an integer and h is Planck's constant; the internuclear distance r then follows from the well-known expression $I = \frac{m_1 m_2}{m_1 + m_2} r^2$, where m_1 and m_2 are the masses of the atoms. The observation of pure rotation spectra is very difficult on the experimental side, however, and a balance between difficulties of experiment and interpretation is found in the vibration-rotation spectra for which, to a good degree of approximation, $\nu = \omega_0 + nh/4\pi^2 I$, where ω_0 is the fundamental vibrational frequency of the molecule. It is evident that, as the number of atoms in a molecule increases above two, there is a corresponding increase in the complexity of the spectra of all types.

Even greater importance attaches to the study of the effect first observed by Sir C. V. Raman in 1928, though predicted by Smekal at an earlier date.[8] When a beam of monochromatic light falls on a transparent substance—solid, liquid, or gas—the greater part undergoes no change of frequency, but at the same time a small proportion appears with a modified (usually smaller) frequency. The incident light quantum changes (as a rule raises) the energy level of a

[8] Raman and Krishnan, *Nature*, 1928, **121**, 501; *Indian J. Physics*, 1928, **2**, 399. See also Kohlrausch, *Der Smekal-Raman Effekt* (Springer, Berlin, 1931). Useful summaries are as follows; Raman, *Trans. Faraday Soc.* 1929, **25**, 781; Hunter, *Ann. Reports*, 1929, **26**, 16; Woodward, ibid. 1934, **31**, 21. For a collection of Raman spectra data see *Chem. Reviews*, 1933, **13**, 345; 1936, **18**, 1.

molecule, atom, or ion which it encounters, with a corresponding change in its own energy content and therefore frequency,[9] i.e.

$$\underset{\text{(normal)}}{\text{Molecule}} + \text{Radiation} \rightleftarrows \underset{\text{(excited)}}{\text{Molecule}} + \underset{\text{(degraded frequency)}}{\text{Radiation.}}$$

The difference between the frequencies of the initial and scattered radiation is called the Raman Frequency, and is governed *solely* by the nature of the molecule. As a rule the energy transferred is utilized completely in raising the vibrational level, and hence the Raman spectrum is not complicated by rotational changes; the Raman effect, indeed, makes possible the observation of the '*Q* branch' of the vibration-rotation spectrum without the experimental difficulties of working in the infra-red. Rotational changes, which sometimes occur, are indicated by lines of frequency very near to that of the exciting radiation.

Raman spectra have been employed in qualitative and even quantitative analysis, and in investigations of the degree of ionization of electrolytes. In the case of molecules of organic compounds, particular lines have been identified with definite linkages, and the natural vibrational frequencies of bonds such as C—H, C=C, C=O, C≡C, and C≡N are thus calculated; in general, those of the two-, four-, and six-electron bonds are of the order of 3,000, 1,600, and 2,000 cm.$^{-1}$ respectively, and observations of Raman spectra have thus given information regarding the multiplicity of certain linkages.[10] Moreover, since the vibrational frequency is dependent upon the masses of the atoms concerned and upon the force constant of the linkage (the force which comes into play when the nuclei are displaced unit distance from their normal positions), the latter can be determined. Its significance lies in the fact that it is a measure of the strength of the bond.

The replacement of an element by its isotope leaves the force constant of the linkage practically unchanged, and the effect of such substitution upon the vibrational frequencies is therefore due to the change in the atomic mass. It is thus possible to calculate numerical relationships between the frequencies of vibration in the two molecules and to compare them with those observed. This method has recently been employed by Ingold and his collaborators[11] in a series of investigations upon the structure of benzene, in which its infrared and Raman spectra have been compared with those of hexadeuterobenzene, C_6D_6 (where D represents deuterium, the heavy isotope of hydrogen).

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[9] Comparison with the photoelectric and Compton effects is instructive. In the former the quantum is *completely* absorbed and ejects an electron from an atom with considerable velocity; in the latter the quantum gives up a portion of its energy to an *electron* and appears with a degraded frequency (see Chap. I, p. 12).

[10] An example is given in Chap. VIII.

3. *Electron Diffraction*[12]

The X-ray method of investigating molecular structure was extended by Debye[13] to include the study of the interference figures produced when X-rays are scattered by the molecules of a gas. A procedure of the same type, substituting fast-moving electrons (cathode-rays) for the X-rays, has been devised by Wierl,[14] and, largely in the hands of Pauling and Brockway,[15] has given results of considerable interest and importance.

The diffraction of electrons was first observed by Davisson and Germer[16] and by G. P. Thomson,[17] who thus provided experimental justification for the concepts of the new wave-mechanics, and Wierl's method employs this proved similarity in behaviour between electrons and X-rays. A fine beam of fast-moving electrons is passed at right angles through a narrow stream of the gas under low pressure; the electrons are scattered, and then record an interference pattern on a photographic plate. The necessary time of exposure is only a fraction of a second, and the method is thus applicable to a much wider range of compounds than is Debye's X-ray scattering. The latter requires an exposure of several hours at ordinary pressure and an impossibly long period at lower pressures, and is therefore useless for substances which do not vaporize at ordinary pressures without decomposition.

The values of internuclear distances obtained by the electron-diffraction method are in good agreement with those found spectroscopically. Light has also been thrown on the structure of various molecules, as exemplified in a later chapter.[18]

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[11] *J.C.S.* 1936, 912, and following papers.

[12] For summaries of this subject and references to original literature see Glasstone, *Recent Advances in General Chemistry* (Churchill, 1936), Chap. V; *Ann. Reports*, 1936, **33**, 65.

[13] *Physikal. Z.* 1929, **30**, 84, and later papers.

[14] Mark and Wierl, *Z. Physik*, 1930, **60**, 741.

[15] See numerous papers from 1933 onwards.

[16] *Phys. Rev.* 1927, **30**, 705.

[17] *Proc. Roy. Soc.* 1928, **117** A, 600; **119** A, 651.

[18] See Chap. VIII.

4. *Dipole Moments*[19]

In Sugden's formula for the nitro-group[20] the co-ordinate bond is obviously dipolar, the nitrogen atom being charged positively and one of the oxygens negatively; this is, indeed, a general property of co-ordinate bonds formed between neutral atoms or molecules, since one atom gives and the other accepts a share in an electron pair.[21] Dipolar character is not peculiar to co-ordinate bonds, however. Thus, the chemical behaviour of the carbonyl group indicates that the carbon and the oxygen are positive and negative respectively; for example, in an addition reaction such as cyanohydrin formation, hydrogen always attaches itself to oxygen and the anionic portion of the addendum unites with carbon. Chemical evidence would thus lead to the representation $>\overset{\delta+}{C}=\overset{\delta-}{O}$, where $\delta+$ and $\delta-$ denote fractional positive and negative charges respectively.

The unequal sharing of the electron pair forming a covalent bond was postulated by G. N. Lewis. This has already been referred to as the origin of the Inductive Effect,[22] but it will be useful again to quote his words here. Lewis wrote:[23] 'the pair of electrons which constitutes the bond may lie between two atomic centres in such a position that there is no electric polarization, or it may be shifted toward one or the other atom in order to give to that atom a negative, and consequently to the other atom a positive charge.' If the latter be the case, the bond is an electrical dipole,[24] equivalent to a rod with equal and opposite charges at the ends; such a rod has an electric moment given by the product of one of the charges and the distance between them.

Since all molecules contain both positively and negatively charged particles (nuclei and electrons), there will of necessity be an 'electrical centre' (analogous to centre of gravity) of the positive charges and a similar centre of the negative electricity, and if these do not coincide the molecule *as a whole* will be an electrical dipole. The electrical moment will be zero only (*a*) if every pair of electrons is shared equally by the atoms concerned,[25] or (*b*) if the molecule is perfectly symmetrical, like methane, so that the moments cancel. In actual fact, the only completely non-polar bonds are those between like atoms, as in the molecules H_2, N_2, or O_2, and hence the existence of a molecular electric moment is the rule and not the exception.

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[19] For comprehensive accounts of this subject, see Debye, *Polar Molecules* (Chemical Catalog Co., New York, 1929); Smyth, *Dielectric Constant and Molecular Structure* (American Chemical Society Monograph Series, New York, 1931). Summaries may be found as follows: Sidgwick, ref. 6; Glasstone, ref. 6; Smyth, *Chem. Reviews*, 1929, **6**, 549; Williams, ibid., p. 589. A list of dipole moments, with full references (up to 1934), is given in *Trans. Faraday Soc.*, Sept. 1934, appendix.

[20] See Chap. I, p. 7.

[21] A similar remark does not apply, for obvious reasons, to a bond formed by co-ordination of an ion with a neutral molecule as in the ammonium and borofluoride ions. See Sidgwick, *The Electronic Theory of Valency* (Oxford University Press, 1927), p. 69.

[22] Chap. II, p. 30.

[23] *Valence and the Structure of Atoms and Molecules* (Chemical Catalog Co., New York, 1923), p. 83.

[24] This must not be confused with the 'electrovalent' bond. See Sidgwick, *Covalent Link*, p. 126 (footnote).

Measurement of Dipole Moments. The conception of 'polar molecules' was first arrived at on purely physical grounds. Apart from any permanent *polarization* of the type described above, all molecules have a definite *polarizability*. Thus, if the space between two charged plates be filled with any medium, the electric field induces a displacement of the positive and negative electrical centres of the molecules of the medium; they become *temporarily* dipolar, the positive ends being towards the negative pole and vice versa. The electrical field is thus opposed, and the ratio of its strength in a vacuum to its strength under these conditions is the dielectric constant (ϵ) of the medium. The 'molecular polarizability' (α) is then given, according to the well-known Clausius-Mosotti Law, by the expression

$$\frac{\epsilon-1}{\epsilon+2}\frac{M}{d}=\frac{4\pi N}{3}\alpha,$$

where M and d are respectively the molecular weight and density of the substance, and N is the Avogadro Number (number of molecules per gram-molecule). This expression contains no temperature term, and yet in the case of many compounds the value of the fraction on the left-hand side of the Clausius-Mosotti equation was found to vary with temperature; for these compounds, too, Maxwell's Law equating the dielectric constant with the square of the refractive index ($\epsilon = n^2$) was invalid. Accordingly, Debye suggested in 1912[26] that the molecules of these substances are permanently dipolar. The dipoles are normally oriented at random, but in an electric field they tend to aline themselves with their ends towards the oppositely charged pole. Thus, the permanent polarization is superimposed upon the induced polarization, $P = P_I + P_\mu$. The term P_I in this expression is that given by the Clausius-Mosotti equation, and since the orientation of the dipoles will be opposed by thermal agitation the second term P_μ is dependent upon temperature. Debye thus arrived at a mathematical relationship of the form $P = A + B/T$, the complete expression being

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[25] This is really a simplified statement of the necessary conditions. The *unshared* electrons must also be arranged symmetrically with respect to their nuclei; compare Sidgwick, op. cit., p. 143 (footnote).

[26] *Physikal. Z.* 1912, **13**, 97.

$$\frac{\epsilon-1}{\epsilon+2}\frac{M}{d} = \frac{4\pi N}{3}\left(\alpha+\frac{\mu^2}{3kT}\right),$$

where μ is the dipole moment of the molecules, T is absolute temperature, and k is the gas constant per molecule ($k = R/N$).

The dipole moments of a large number of molecules have now been determined. The most accurate method depends upon the effect of temperature upon the dielectric constant of the substance in the vapour state. In Debye's equation $P = A + B/T$, the relationship between P and $1/T$ is linear; if the substance is non-polar, $B = 0$ and the line is parallel to the $1/T$ axis, while for a polar molecule its slope gives the value of $4\pi N\mu^2/9k$. Attempts have been made to apply this method to solutions in non-polar solvents, but the results are inaccurate.[27]

The gas-temperature method has the disadvantage that the range of temperature required for accuracy is rather large, and many organic substances are not stable over this range. An alternative procedure, the optical method, has therefore been employed more frequently. Using Maxwell's relation $\epsilon = n^2$, the Clausius-Mosotti equation can be written

$$\frac{n^2-1}{n^2+2}\frac{M}{d} = \frac{4\pi N}{3}\alpha$$

(compare the Lorenz-Lorentz expression for molecular refraction). The refractive index is determined for visible light, i.e. for vibrations of relatively high frequency, and the polar molecules will not, under these conditions, have time to orient themselves between one wave and the next. The difference between the total polarization P (obtained from the dielectric constant) and the induced polarization P_I (from the refractive index) should therefore give the permanent polarization P_μ. An error arises, however, from the fact that the induced polarization itself is in reality the sum of two terms. In the determination of the dielectric constant, the electrical field displaces the electrons towards the positive pole, giving the electron polarization P_E, but at the same sime the nuclei suffer a small displacement leading to the atom polarization P_A, i.e. $P_I = P_E + P_A$. Like the orientation of the permanent dipoles, the atom polarization does not occur under the agency of visible light, and hence the difference between the values obtained by dielectric constant and refractive index observations actually gives $P_\mu + P_A$. As a rule the atom polarization is not very large in comparison with the electron polarization, and a correction made on the assumption that P_A is 5 per cent. of P_E has been found satisfactory in many instances.[28] The atom polarization is sometimes much larger than this, however.[29]

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[27] Jenkins, *Trans. Faraday Soc.* **1934, 30,** 739.

The values of dipole moments are all of the order 10^{-18} e.s.u.; this would be anticipated, since the unit electronic charge is $4{\cdot}77 \times 10^{-10}$ e.s.u., and molecular distances are of the order 10^{-8} cm. 1×10^{-18} e.s.u. is spoken of as 1 Debye unit, and written D.[30]

Many of the available dipole moment values have been obtained by measurements in solution, and they vary somewhat with the nature of the solvent.[31] The true value of the moment must be regarded as that given by the vapour, and accurate data referring to the vapour phase are accumulating. Values determined in the same solvent are no doubt comparable, however, and are used in the sequel in cases where the moment of the vapour is not available (and sometimes, indeed, cannot be found owing to decomposition).

Sign of Dipole Moments. The methods outlined above provide values for the *magnitudes* of dipole moments, but give no information with regard to their *sign*; they do not indicate which atom forms the positive end and which the negative end of the dipole, i.e. no distinction is drawn between $\overset{+}{X}—\overset{-}{Y}$ and $\overset{-}{X}—\overset{+}{Y}$. An ingenious method of ascertaining this further fact for the bond linking a substituent to

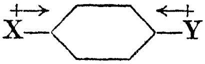
[28] Groves and Sugden, *J.C.S.* 1935, 971; 1937, 158, 1779, 1782.

[29] Coop and Sutton, ibid. 1938, 1269.

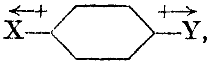
[30] An approximate method for determining dipole moments, which is sometimes applicable where the others fail, is an adaptation of the Stern and Gerlach process for the determination of magnetic moments (see p. 64). A fine beam of molecules emerging through a slit from a tiny oven is passed, under high vacuum, through a highly inhomogeneous electric field and received on a brass plate cooled by liquid air. The moment of the molecule is indicated by the broadening of the trace produced on the plate. A useful summary of this method is given in Dole, *Experimental and Theoretical Electrochemistry* (McGraw-Hill Book Co., New York, 1935), p. 195.

[31] See Glasstone, *Annual Reports*, 1936, 33, 117; ref. 6, p. 144.

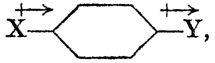
nuclear carbon in an aromatic compound was suggested by Sir J. J. Thomson[32] and worked out by J. W. Williams.[33] The absence of a resultant dipole moment in unsubstituted benzene is accounted for by the symmetrical character of the aromatic nucleus. Since moments are directed magnitudes, the value for a disubstituted derivative C_6H_4XY should be the vector sum of the individual moments of the C—X and C—Y bonds (making the assumption which, however, is only approximately true, that the value for any particular bond is unaffected by other bonds in the molecule). If the nucleus is flat,[34] the moments of the bonds linking the carbon atoms to two groups in *p*-positions will be in a straight line, and hence the resultant is in this case the arithmetic sum or difference of the two bond moments. When the directions of the moments with respect to the ring are the same as in[35]



or



they will oppose, and the resultant will be approximately the difference of those produced by each group when present alone (i.e. of C_6H_5X and C_6H_5Y); when the directions are opposite, however, as in



they will reinforce, and the observed moment of C_6H_4XY will be the sum of those of C_6H_5X and C_6H_5Y. In accordance with this view, it is found that *p*-dialkyl-, *p*-dihalogeno-, and *p*-dinitro-benzenes have dipole moments which are indistinguishable from zero, and the same remark applies to the symmetrical trialkyl- and trihalogeno-benzenes (and probably to *s*-trinitrobenzene); the flat configuration of the aromatic nucleus is thus confirmed.

Among derivatives with two *different* substituents in *p*-positions, the observed values for *p*-nitrotoluene and *p*-nitrochlorobenzene show that the former is very nearly the *sum* of the moments of toluene and nitrobenzene, while the latter is approximately the *difference* of those of chlorobenzene and nitrobenzene. Examples of this kind make it possible to divide the bonds into two classes; C—NO_2 and C—Halogen fall into one, and C—Alkyl into the other, and the direction of the dipole is different in the two classes. It remains to determine which class has the positive end of the dipole on carbon, and vice versa, and this can be done from other considerations. The clearest indication is perhaps given by the known structure of the nitro-group, from which it is obvious that the direction of the C—NO_2 dipole is away from the ring, $\overset{+\longrightarrow}{\text{C—NO}_2}$. Hence, for the other groups the directions are $\overset{+\longrightarrow}{\text{C—Halogen}}$ and $\overset{\longleftarrow+}{\text{C—Alkyl}}$. It is conventional to denote moments having the direction $\overset{\longleftarrow+}{\text{C—X}}$ (e.g. C—Alkyl) by a positive sign and those having the reverse direction, $\overset{+\longrightarrow}{\text{C—Y}}$ (e.g. C—NO_2, C—Hal.), by a negative sign. Thus the dipole moment of toluene is $+0{\cdot}37$ D, while those of nitrobenzene and chlorobenzene are $-4{\cdot}24$ D and $-1{\cdot}73$ D respectively. The positive sign indicates that the group X is electron-repulsive, while the negative sign denotes electron-attractive character on the part of the group Y; groups such as X lower the dissociation constants of acids in which they are substituted, whereas groups of the nature of Y have the opposite influence (see Chap. II).

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[32] *Phil. Mag.* 1923, **46**, 497.

[33] *Physikal. Z.* 1928, **29**, 174.

[34] Compare p. 44.

[35] The arrow indicates the direction in which the electrons are displaced from a perfectly symmetrical position with respect to the two nuclei; the head of the arrow therefore points towards the negative end of the dipole, and the tail denotes its positive end. This notation is used by Sidgwick.

Dipole Moments of Aliphatic Compounds. The symmetrical hydrocarbons methane, ethylene, and acetylene have zero moment. The same applies, indeed, to all the paraffins; it has been demonstrated for the straight chain members up to *n*-dodecane, and for all the nine isomeric heptanes. It is no doubt correct to assume that the C—C bond is non-polar, but this does not necessarily apply to the C—H bond;[36] methane is completely non-polar on account of symmetry. Since, however, any paraffin can be derived from methane by successive replacements of H by CH_3, it is evident that such replacements do not endow the molecule with a permanently polar character. Members of other homologous series also have moments which show hardly any perceptible difference; the moments of primary alcohols with carbon atoms numbering from one to twelve are all between 1·6 D and 1·7 D, and those of secondary and tertiary alcohols differ but little from this value; ketones from acetone to methyl nonyl ketone all have moments of approximately 2·8 D, and nitroparaffins up to C_4 give a practically constant value. The moments of homologous alkyl chlorides reach a limiting value at C_3, but bromides and iodides (especially the latter) have moments which increase beyond this point.[37] The moments of homologous series are discussed further in Chapter VI. Carbon tetrachloride, being symmetrical, has zero moment, and a fall in moment from methyl chloride to chloroform is due to the neutralizing effects of the dipoles.[38]

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[36] Sidgwick accepts 0·2 D as the most probable moment for this bond. The reader is referred to his very clear discussion of this and other bond moments in *The Covalent Link*, pp. 141–53.

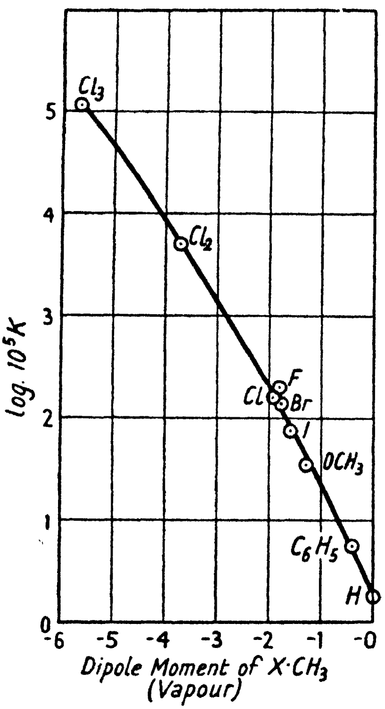

FIG. 5.

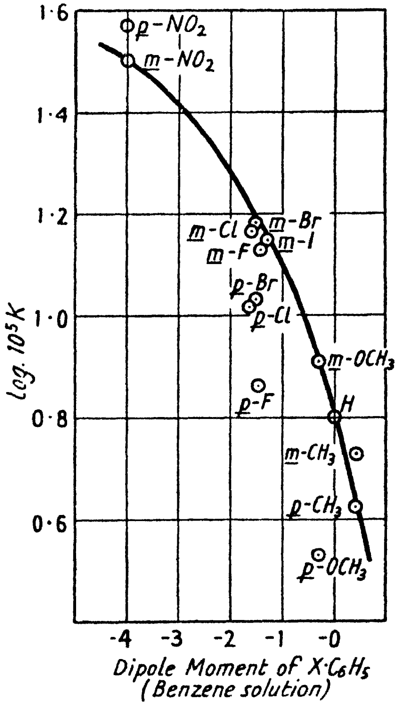

FIG. 6.

Relationship of Dissociation Constants of Acids to Dipole Moments of Substituted Hydrocarbons.

FIG. 5. Acetic Acids, $X \cdot CH_2 \cdot COOH$.
(Nathan and Watson, *J.C.S.* 1933, 894)

FIG. 6. Benzoic Acids, $X \cdot C_6H_4 \cdot COOH$.
(Dippy and Watson, *J.C.S.* 1936, 438)

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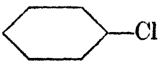
[37] Groves and Sugden, *J.C.S.* 1937, 158; Cowley and Partington, *J.C.S.* 1933, 1252; 1935, 604.

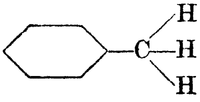
[38] Sutton and Brockway, *J. Amer. Chem. Soc.* 1935, **57**, 473.

It is evident that the same property of a group, viz. its electron-attractive or -repulsive character, is under observation whether the physical constant measured be the dipole moment of a substituted hydrocarbon or the dissociation constant of a carboxylic acid. Among aliphatic compounds, indeed, where the group is attached to a saturated carbon atom, either set of data may be taken as a measure of Inductive Effects.[39] It is thus to be expected that some quantitative relationship should exist between dissociation constants and dipole moments, and such a relationship has actually been observed.[40] By plotting the logarithms of the dissociation constants of a series of substituted acetic acids, $X \cdot CH_2 \cdot COOH$, against the dipole moments of the corresponding substituted methanes, $X \cdot CH_3$, a smooth curve is obtained, as shown in Fig. 5. This curve can be represented by the equation $\log K = \log K_0 - C(\mu + a\mu^2)$, where K_0 is the dissociation constant of the unsubstituted acid ($X = H$) and C and a are constants for the series. The only data available for testing the expression are Ostwald's classical constants, but the inaccuracies are unimportant in view of the wide range covered. This relationship recalls Derick's expression for the 'negativity' of a substituent as a logarithmic function of the dissociation constant of the appropriate acid;[41] it is actually a connexion between dipole moments and changes in free energy of ionization.

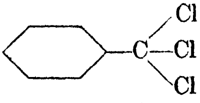
Dipole Moments of Aromatic Compounds. The resultant moment of benzene, like that of methane, is zero owing to the symmetry of the molecule. Similarly, a number of *p*-disubstituted and *s*-trisubstituted benzene derivatives have zero moment, while the corresponding monosubstituted compounds are definitely polar:



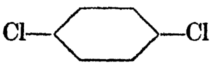
$\mu = 1{\cdot}73$



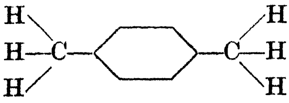
$\mu = 0{\cdot}37$



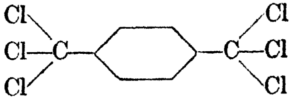
$\mu = 2{\cdot}07$



$\mu = 0$



$\mu = 0$



$\mu \neq 0$

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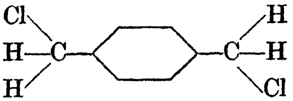
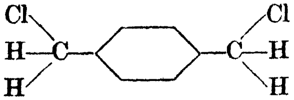
[39] The case of alkyl groups, which give no moment when linked to saturated carbon in hydrocarbons, is discussed in Chap. VI. It may be pointed out here, however, that it is quite correct to designate their effect on the dissociation constants of carboxylic acids as +I.

[40] Nathan and Watson, *J.C.S.* 1933, 893.

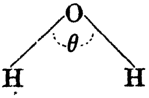
[41] See p. 30.

Other compounds having two identical substituents in *p*-positions have quite large moments, however. One of these is *p*-xylylene dichloride, $C_6H_4(CH_2Cl)_2$, for which $\mu = 2{\cdot}2$ D. The free rotation of the $-CH_2Cl$ groups about the bonds linking them to the nucleus makes possible any structural configuration between the extremes I and II, and of all these only that represented by I is non-polar.

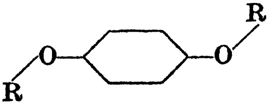

I.

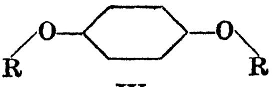

II.

It is important to realize that, in contrast with a case of this kind, all the possible configurations of *p*-xylene or *p*-$Cl_3C \cdot C_6H_4 \cdot CCl_3$ (above) are identical and non-polar. A relatively high resultant moment is also found in *p*-disubstituted compounds where oxygen is linked to the nucleus, as illustrated by the dialkyl ethers and diacetate of hydroquinone, where μ is of the order 2 D. This is due to the arrangement of the valencies of oxygen. The value of 1·84 D for the moment of water indicates a 'triangular' structure,



since a linear molecule, H—O—H, would be non-polar. The most probable value for the angle θ between the oxygen valencies, as determined by spectroscopic measurements, is 105°–110°.[42] The hydroquinone derivatives referred to above could take up any configuration between III and IV (below), III alone being non-polar. Dialkylterephthalates ($\mu = 2{\cdot}2$) and *p*-phthalaldehyde $C_6H_4(CHO)_2$ ($\mu = 2{\cdot}35$) are similarly capable of an infinite number of configurations of which only one extreme is non-polar. Fairly large moments have also been observed in *p*-phenylenediamine (1·5) and its tetramethyl derivative (1·2), where trivalent nitrogen is linked to the nucleus. Ammonia itself has a definite moment ($\mu = 1{\cdot}5$), in harmony with a multiplanar


III.


IV.

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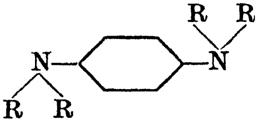
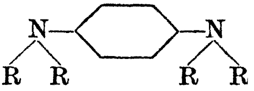
[42] Mecke (*Trans. Faraday Soc.* 1934, **30**, 90) gives 105° 6′.

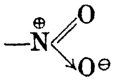
configuration of the atoms (a tetrahedron with nitrogen at the apex), and the results of infra-red spectroscopy again indicate a valency angle not far from 110°.[43] The extreme positions for *p*-phenylenediamine may be written as in V and VI, and of all the possible structures only V is non-polar.

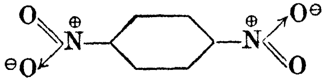

V.

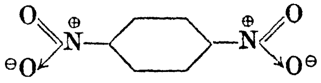

VI.

In all these compounds the *average* configuration will be intermediate between the two extremes, and it is therefore to be expected that the measured moment should be considerable, but less than that calculated for the most polar form. This is in harmony with observation.

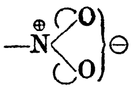
If the nitro-group were correctly represented by the structure VII, a resultant moment would be anticipated for *p*-dinitrobenzene, which could assume any configuration between the extremes VIII and IX, the former of which is non-polar and the latter highly polar.

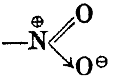

VII.


VIII.


IX.

Actually, however, *p*-dinitrobenzene is non-polar, and the inevitable conclusion is that the nitro-group is symmetrical owing to resonance. The mesomeric state (X) is related equally to the structures XI and XII.


X.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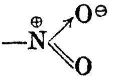
XII.

Mesomeric Moments. A matter of very considerable interest and importance is the difference between the value of the dipole moment of an aliphatic compound *Alphyl X* and that of the corresponding aromatic compound *Aryl X*. Table I illustrates the differences which are found: the values quoted are from the list in *Trans. Faraday Soc.*, Sept. 1934, Appendix, or from later papers of Groves and Sugden[28] or of Cowley and Partington.[37] Whenever possible, values are given both for the vapour and for benzene solution.

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[43] Dennison and Uhlenbeck, *Phys. Rev.* 1932, **41**, 313.

TABLE I

Dipole Moments of Aliphatic and Aromatic Compounds

	Solution	*Vapour*		*Solution*	*Vapour*
CH_4	..	0	C_6H_6	0	0
$CH_3{\cdot}CH_3$	..	0	$C_6H_5{\cdot}CH_3$	0·41	0·37
$CH_3{\cdot}OH$	1·68	1·69	$C_6H_5{\cdot}OH$	1·61	1·40
$CH_3{\cdot}O{\cdot}CH_3$	..	1·31	$C_6H_5{\cdot}O{\cdot}CH_3$	1·16	1·35
$CH_3{\cdot}F$	..	1·81	$C_6H_5{\cdot}F$	1·45	1·57
$CH_3{\cdot}Cl$	..	1·87	$C_6H_5{\cdot}Cl$	1·56	1·73
$CH_3{\cdot}Br$	..	1·80	$C_6H_5{\cdot}Br$	1·53	1·71
$CH_3{\cdot}I$	1·60	1·64	$C_6H_5{\cdot}I$	1·30	..
$CH_3{\cdot}CHO$	..	2·70	$C_6H_5{\cdot}CHO$	2·75	..
$CH_3{\cdot}CO{\cdot}CH_3$	2·76	2·85	$C_6H_5{\cdot}CO{\cdot}CH_3$	2·93	3·00
$CH_3{\cdot}COOC_2H_5$	1·85	1·76	$C_6H_5{\cdot}COOC_2H_5$	1·92	1·95
$CH_3{\cdot}CN$	3·44	3·94	$C_6H_5{\cdot}CN$	3·90	4·37
$CH_3{\cdot}NO_2$	3·02	3·54	$C_6H_5{\cdot}NO_2$	3·97	4·24
$CH_3{\cdot}NH_2$	..	1·32	$C_6H_5{\cdot}NH_2$	1·52	1·48
$CH_3{\cdot}N(CH_3)_2$	..	0·65	$C_6H_5{\cdot}N(CH_3)_2$	1·58	1·61

Sutton has pointed out a relationship between the directive influence of a group X and the sign of the difference between the moments of *Aryl X* and *Alphyl X*.[44] If, using the conventional positive and negative signs for the moments, the difference ($\mu_{\text{Aryl X}}-\mu_{\text{Alphyl X}}$) is positive, then X is *op*-directive; if it is negative, X is *m*-directive. In order to make the moments comparable, Sutton uses, when values are available, those of aliphatic compounds where the group X is linked to tertiary carbon;[45] the possibilities of induced polarization in bonds adjacent to C—X are then as nearly as possible equal. Table II illustrates Sutton's relationship; all the values recorded are for solutions in benzene.

TABLE II

Group X	$\mu_{\text{Aryl X}}$	$\mu_{\text{Alphyl X}}$	*Difference*	*Directive influence*
CH_3	+0·41	0	+0·41	*op*
Cl	−1·56	−2·15	+0·59	*op*
Br	−1·53	−2·21	+0·68	*op*
I	−1·30	−2·13	+0·83	*op*
CH_2Cl	−1·82	−2·14	+0·32	*op*
CN	−3·90	−3·46	−0·44	*m*
NO_2	−3·97	−3·29	−0·68	*m*

Groves and Sugden have more recently drawn up a similar table employing values measured in the vapour state; for $\mu_{\text{Alphyl X}}$ they use the limiting values to which the moments of the homologous series *n-Alphyl X* tend.[46] Their table is reproduced as Table III.

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[44] *Proc. Roy. Soc.* 1931, **133 A**, 668.

[45] For example, Alphyl Cl is *tert*-butyl chloride. This accounts for the fact that the moments of the alphyl compounds in Table II are not identical with those in Table I.

TABLE III

Group X	$\mu_{\text{Aryl X}}$	$\mu_{\text{Alphyl X}}$	*Difference*	*Directive influence*
F	−1·57	−1·92	+0·35	*op*
Cl	−1·73	−2·04	+0·31	*op*
Br	−1·71	−2·08	+0·37	*op*
CN	−4·37	−4·07	−0·30	*m*
NO_2	−4·24	−4·03	−0·21	*m*
$CO\cdot CH_3$	−3·00	−2·80	−0·20	*m*

The vapour values confirm Sutton's generalization, although the differences are smaller than for the moments found in solution.

It has been pointed out in preceding chapters that the dissociation constants of aromatic acids and the facts relating to aromatic substitution show quite clearly that the total influence of a group linked to the benzene nucleus includes some other factor in addition to its inductive effect. This is confirmed by the differences in the values of the dipole moments of aromatic compounds and their aliphatic analogues. Further, the electronic displacements which constitute this further effect are permanent, since their influence is found in dipole moments and in ionic equilibria (in both of which the normal or resting state of the molecule is concerned), and not only in chemical reactions (where 'time-variable' factors might operate at the demand of a given reagent). Sutton's rule shows also that these permanent electronic displacements are in the direction necessary for the directive influence of the group, being away from it when substitution is *op* and towards it when substitution is *m*. It must not be assumed, however, that the permanent effects are solely responsible for the influences of groups upon substitution processes, since at the moment of reaction the molecule will behave in accordance with the sum of time-variable and permanent factors. This point is considered further in Chapter VI.

That portion of the total moment of an aromatic compound which is not found in the aliphatic analogue (that is, the portion which is distinct from the inductive effect of the group) is termed the 'mesomeric moment'. Values of the mesomeric moments in a number of compounds have been computed, certain assumptions and approximations being made with regard to valency angles and induction within the molecule. Some of the values obtained are recorded in Table IV. A surprising feature is the small value of the mesomeric moment due to a *m*-directive group.

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[46] *J.C.S.* 1935, 973.

TABLE IV

Mesomeric Moments (Debye units)

(*a*) *From measurements on vapours.* Groves and Sugden, *J.C.S.* 1937, 1992.

C_6H_5F	1·00	$C_6H_5OCH_3$	0·40
C_6H_5Cl	0·97	C_6H_5OH	1·20
C_6H_5Br	0·89	$C_6H_5COCH_3$	0·17
C_6H_5I	0·87	$C_6H_5NO_2$	0·29

(*b*) *From measurements in benzene solution.* Marsden and Sutton, *J.C.S.* 1936, 599.

$C_6H_5NH_2$	1·12	$C_6H_5N(CH_3)_2$	1·55

The mesomeric moment due to a given group is not constant in magnitude, but varies from compound to compound. The clearest demonstration of this has been given by Bennett and Glasstone,[47] who dealt with the moments of a number of *p*-substituted derivatives of phenol, anisole, and aniline. They calculated the moment, by vector addition, from those of the appropriate monosubstituted benzenes, and found that the figure so arrived at was never equal to the experimentally determined moment. This is illustrated in Table V. Clearly, the presence of one group influences the value of the moment due to the other; e.g. the moment due to the amino group in *p*-nitroaniline is not identical with that due to the same group in aniline.

TABLE V

Calculated and Experimental Dipole Moments of p-substituted Anisoles and Anilines

X	*Moment of* X⬡OCH_3		*Moment of* X⬡NH_2	
	$\mu_{calc.}$	$\mu_{obs.}$	$\mu_{calc.}$	$\mu_{obs.}$
F	1·34	2·09	2·36	2·75
Cl	1·42	2·24	2·46	2·90
Br	1·40	2·27	2·42	2·87
I	1·27	2·12	2·23	2·82
NO_2	3·47	4·74	4·66	6·20

A further indication of the variation in magnitude of the mesomeric moment is found when quantitative relationships are sought between the dissociation constants of aromatic acids $X \cdot C_6H_4 \cdot COOH$

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[47] *Proc. Roy. Soc.* 1934, **145**, A, 71.

and the dipole moments of the substituted benzenes $X \cdot C_6H_5$. The existence of such a relationship between the dissociation constants of substituted acetic acids and the dipole moments of the aliphatic compounds $X \cdot CH_3$ (see Fig. 5, p. 56) indicates that the same effect is being observed in the moments and the ionic equilibria; this is, of course, the Inductive Effect. When the values of log K for a number of *m*-substituted benzoic acids are plotted against the dipole moments of the compounds $X \cdot C_6H_5$ a smooth curve is again obtained, but there is no such relationship for the dissociation constants of *p*-substituted aromatic acids. The plot is shown in Fig. 6 (p. 56). It must be concluded that the permanent electronic displacements which are responsible for the mesomeric moments of aromatic molecules vary in magnitude from compound to compound (e.g. the displacements to which the nitro-group gives rise are quantitatively different in nitrobenzene and nitrobenzoic acid), these variations being particularly evident in a compound containing two substituents placed in *p*-positions.

The origin and nature of the electronic displacements which give rise to the mesomeric moments of aromatic compounds will be discussed in Chapter VI, and other applications of dipole moment data to the solution of problems of organic chemistry will be recorded in later chapters.

5. *Molecular Magnetism*[48]

Measurements of molecular magnetic susceptibilities have been employed in the detection of free radicals, and a short account of certain magnetic phenomena is therefore given here.

According to Langevin's theory of magnetism (1905), the path of each electron in the atom is equivalent to a magnet of definite moment. When the number of electrons is even, however, the moments may neutralize in pairs, giving a resultant of zero. The electronic movements will then be somewhat modified by an external field, and the phenomenon of diamagnetism arises from this cause. A diamagnetic substance is repelled by a magnet, because a pole of given sign induces a pole of the same sign nearest to itself; when placed between two poles it increases the field strength. This effect is small, independent of temperature (Curie's law), and common to all matter; for a given compound the diamagnetic susceptibility (magnetic moment acquired by unit mass in a field of unit strength) can be calculated as the sum of the values of the atomic and constitutive constants (Pascal). If, however, the electrons are not 'paired' in the magnetic sense, the atom or molecule will have a resultant moment; it is paramagnetic (or, in a few extreme cases, ferromagnetic): it is *attracted* by a magnet, and in a magnetic field will orient itself in such a way as to *reduce* the field strength. The orientation of the molecules is opposed by thermal agitation (compare molecules with permanent electrical dipoles when placed in an electric field), and hence the paramagnetic susceptibility decreases with rise of temperature. When paramagnetism exists, it completely conceals the diamagnetism, on account of its much greater magnitude. The mutual influences of electrons of neighbouring atoms also contribute to the total magnetic susceptibility; the effect is in most cases very small, however, and may be neglected. It is probably responsible for a feeble paramagnetism, not varying with temperature, observed in the permanganates, dichromates, and some complex salts. The molecular magnetic susceptibility is therefore the sum of three terms:

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[48] For full discussions of magnetic phenomena, see Stoner, *Magnetism and Atomic Structure* (Methuen, 1926); Van Vleck, *The Theory of Electric and Magnetic Susceptibilities* (Oxford University Press, 1932). Useful summaries are found as follows: G. N. Lewis, *Valence and the Structure of Atoms and Molecules* (Chemical Catalog Co., New York, 1923), pp. 52 and 147; Sidgwick, *The Electronic Theory of Valency* (Oxford University Press, 1927), p. 204; Sugden, *Trans. Faraday Soc.* 1934, **30**, 18.

$$\chi_M = \chi_d + \chi_\mu + \chi_r.$$

χ_μ, the paramagnetic contribution, when present is large in comparison with χ_d, the diamagnetic contribution, and is determined by subtraction of χ_d, calculated from atomic constants, from the experimentally observed value of χ_M, χ_r being neglected. χ_M is conveniently measured by the Guoy method,[49] which consists in observation of the apparent loss of weight when one end of a column of the substance (which may be contained in a glass tube) is suspended in a magnetic field.

It was pointed out by G. N. Lewis[50] that an atom or molecule having an odd number of electrons should be strongly paramagnetic, and in accordance with this view copper, silver, gold, sodium, and potassium are paramagnetic, while zinc, cadmium, mercury, tin, and lead have no moment.[51] The 'odd molecules' NO, NO_2, and ClO_2

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[49] Described by Sugden, *J.C.S.* 1932, 161.

[50] See ref. 48.

[51] The results were obtained by the Stern and Gerlach method, in which a beam of atoms, proceeding from a furnace containing the metal under examination, passes between the poles of an electromagnet, one of which is wedge-shaped (producing a

are also strongly paramagnetic. The paramagnetism of the oxygen molecule forms a striking exception to the rule that 'even' molecules are diamagnetic; it must clearly contain two electrons which are 'unpaired' in the magnetic sense. Bell and Sugden have shown that the hypophosphates are diamagnetic, and therefore derived from $H_4P_2O_6$ and not from H_2PO_3, which is an odd molecule; the result confirms molecular weight determinations on the ethyl ester.[52]

Free radicals are odd molecules, and therefore should be paramagnetic; the use of this property in their detection is dealt with in Chapter VII.

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highly inhomogeneous field). The apparatus is highly exhausted, and the temperature of the furnace only about 100° above the melting-point of the metal. The beam is finally received upon a photographic plate, and the deflexion caused by the field is thus observed. Stern, *Z. Physik*, 1921, **7**, 249; Gerlach and Stern, *Ann. Physik*, 1923, **74**, 673; Gerlach, ibid. 1925, **76**, 163; Taylor, *Physical Rev.* 1926, **28**, 576.

[52] References to original papers are given by Sugden, ref. 48.

V

KINETIC METHODS[1]

FOLLOWING the pioneer work upon reaction velocities by Wilhelmy, Berthelot and St. Gilles, Harcourt and Esson, and others, the Law of Mass Action was enunciated by Guldberg and Waage in 1867, and the science of chemical kinetics as we have it to-day is built upon the foundation laid by these earlier investigators. Kinetic studies have contributed very materially to our knowledge of the reactions of organic compounds; they have thrown a great deal of light upon the mechanisms of many important processes, upon the influences of substituent groups, and upon other problems, even those of stereochemistry. The vast majority of kinetic investigations have consisted in studies of the dependence (or otherwise) of the velocity upon the concentrations of the reagents, or of the relative speeds at which the individual members of a series of similar compounds take part in a given reaction, and in this work measurements have usually been conducted under fixed conditions, e.g. at a single temperature. Examples of the valuable results which have been achieved by this method are to be found throughout this book. It has nevertheless become evident now that, in many cases, an investigation of this kind does not go far enough. We do not take full advantage of the usefulness of the kinetic method of study if we restrict ourselves to work under one set of conditions, and we may, indeed, be led to wrong conclusions. A very striking example of the inadequacy of single temperature measurements in certain cases is provided by some determinations of the speeds of acid hydrolysis of the ethyl esters of the chlorinated acetic acids, carried out by Timm and Hinshelwood.[2] The velocity coefficients (10^5k at 80°) are given below, and underneath are the values of the dissociation constants of the corresponding acids (10^5K).

	Acetate	*Chloroacetate*	*Trichloroacetate*
10^5k	316	226	217
10^5K	1·8	155	121,000

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[1] For a general account of the subject of chemical kinetics, see Hinshelwood, *The Kinetics of Chemical Change* (Oxford University Press, 1940).

[2] *J.C.S.* 1938, 862.

The substituent chlorine atoms have a powerful influence upon the strength of the acid, but make relatively little difference to the speed of hydrolysis of the ester. This strange observation becomes intelligible if we remember that the measured velocity indicates the resultant influence of more than one factor, and that the effects of the substituent chlorine atoms upon the different factors may compensate one another. This is actually what is found upon further investigation, and the example serves to emphasize the point that the kinetic study of the reaction is not complete until some effort has been made to disentangle the factors involved. Only in this way can we extract additional and more definite information from the experimental results, and in order to do this we have to inquire more fully into the manner in which a chemical reaction takes place and the conditions which make it possible. Some of the knowledge that has been gained by such inquiries is summarized in the sections which follow.

Reactions in the Gas Phase. The simplest possible view of the manner in which two substances *A* and *B* interact would be to suppose that a chemical change occurs every time a molecule of *A* comes into collision with a molecule of *B*, but such a conception is rendered untenable by the results of kinetic studies. Thus, the velocities of bimolecular reactions in the gaseous phase are smaller by many powers of ten than the number of collisions as calculated from the kinetic theory,[3] and this leads inevitably to the conclusion that the collisions which actually produce chemical change form only a very small proportion of the total number occurring. It would appear, therefore, that only those molecules which are in some exceptional state can enter into reaction, a view which receives confirmation from the fact that *unimolecular* reactions can proceed at measurable speeds. Again, the temperature coefficients of chemical reactions are of far greater magnitude than can be accounted for on the basis of the increased speeds of the molecules, and it may further be concluded, therefore, that the attainment of the exceptional state is strongly favoured by increasing temperature, the reactive molecules being those of high energy content.

This view was first expressed by Arrhenius in 1889.[4] He found that the variation of reaction velocity with temperature could be represented by an expression of the form $\log k = B - A/T$, where T is the absolute temperature and A and B are constants for the particular reaction under consideration. Writing $A = E/R$, where R is the gas constant, the equation becomes $\log k = B - E/RT$, or $d \log k/dT = E/RT^2$. This expression shows an obvious resemblance to the van 't Hoff Isochore, which represents the effect of temperature upon the *equilibrium* constant of a balanced reaction, and Arrhenius postulated an equilibrium between 'active' and 'normal' molecules, of which the former alone were capable of reaction. E is termed the 'critical increment of energy' or 'energy of activation', and is identified with the energy absorbed in the formation of an active molecule from a normal molecule; it can be determined experimentally from the slope of the straight line obtained by plotting $\log k$ against $1/T$.

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[3] For example, the velocity of decomposition of hydrogen iodide, $2HI \rightarrow H_2+I_2$, is of the order 10^{17} mols. per litre per sec. (Bodenstein, *Z. physikal. Chem.* 1899, **29**, 295), while the number of collisions is of the order 10^{34}.

[4] *Z. physikal. Chem.* 1889, **4**, 226.

A notable advance was made by W. C. McC. Lewis when, in 1918, he calculated the absolute velocities of some gaseous bimolecular reactions on the basis of the concept of activation.[5] The Arrhenius equation may be written in the form

$$k = \alpha e^{-E/RT}, \tag{1}$$

where the exponential term, according to the Maxwell-Boltzmann Distribution Law, gives the fraction of the molecules which have energy E in excess of the average energy of all the molecules. Lewis therefore assumed that

$$\text{no. of effective collisions} = (\text{total no. of collisions}) \times e^{-E/RT},$$

and proceeded to calculate the velocities of the decomposition of hydrogen iodide and the union of hydrogen and iodine; E was determined from the temperature coefficients found by Bodenstein, and the number of collisions from the formulae based on the kinetic theory. The values so obtained were in very good agreement with the experimental results, and a similar agreement has been found in a considerable number of other instances. Indeed, for the majority of homogeneous[6] *gaseous* bimolecular reactions which have been investigated, the non-exponential term of the Arrhenius equation is given, to a high degree of approximation, by the collision frequency Z as calculated from the kinetic theory, i.e. $k = Ze^{-E/RT}$.

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[5] *J.C.S.* 1918, **113**, 471.

[6] i.e. occurring uniformly throughout the gas, and not specifically at the walls of the containing vessel.

Of all the conditions upon which the occurrence of a chemical reaction may depend, therefore, the most important is the possession by the colliding molecules of a quantity of energy which is not less than the energy of activation for the particular process concerned; for gaseous bimolecular reactions this condition is very frequently sufficient. The value of E for reactions which proceed with measurable speeds at temperatures within the range of experiment varies between 15,000 and 60,000 calories. Of recent years a number of homogeneous *unimolecular* gaseous reactions have been discovered, mainly by Hinshelwood and his collaborators; the conception of activation by collision is applicable here also, provided it be assumed that a period of time elapses between the collision and the moment of chemical transformation.[7]

The Inner Mechanism of a Chemical Change.[8] The energy of a molecule has a minimum value when the nuclei are at certain 'equilibrium' distances apart; when they vibrate, the distances are sometimes smaller and sometimes greater than these. A diatomic molecule provides the simplest case, of course. If, starting from their equilibrium positions, the nuclei of such a molecule approach each other, they will oppose a rapidly increasing force which resists compression, and the energy of the molecule rises; if, on the other hand, they move away from each other, work is done in separating them, and the energy again increases, at first rapidly and then more slowly as the forces between them become weaker. With increasing distance, therefore, the energy approaches a constant limiting value, at which complete dissociation occurs. These energy variations are shown in Fig. 7; O represents the equilibrium position, and the height d is a measure of the energy of dissociation of the molecule.[9] The values of the energies of activation of chemical reactions indicate, however, that they do not proceed by way of complete dissociation;

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[7] See Hinshelwood, *Kinetics*. The reactions include the decomposition of nitrogen pentoxide, of acetone, of propionic aldehyde, and of certain ethers. The present view was first expressed by Lindemann, *Trans. Faraday Soc.* 1922, **17**, 598.

[8] See Polanyi, *Atomic Reactions* (Williams and Norgate, London, 1932), chap. i.

[9] The rupture of a linkage occurring as represented in Fig. 7 is termed an 'adiabatic' process, i.e. one in which no change in electronic energy occurs. If the compound is raised to a higher electronic level, its potential energy curve lies above that shown, the minimum energy point usually being to the right of O. Dissociation is frequently observed in electronic band spectra. The absorption of a light quantum of sufficiently high frequency raises the electronic level to a point at which the amplitude of vibration is great enough to cause dissociation, one of the atoms being in an electronically activated state; the spectrum now becomes continuous. See Hinshelwood, *Kinetics*, p. 66.

thus, the energy of activation for the thermal decomposition of hydrogen iodide is 44,000 calories, whereas dissociation into hydrogen and iodine atoms would require about 70,000 calories.[10]

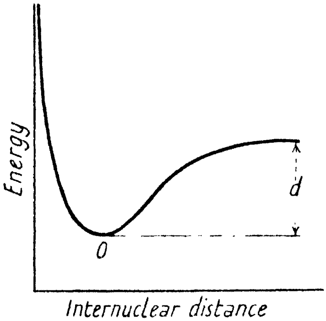

Fig. 7.

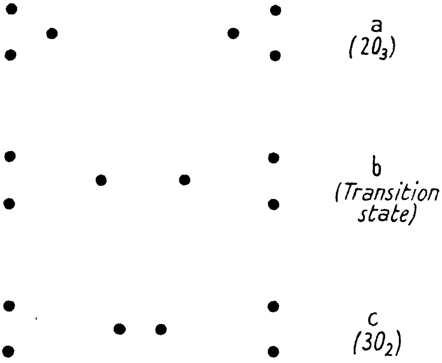

Fig. 8.

A very illuminating picture of the inner mechanism of chemical change has been given by Polanyi, taking the change $2O_3 \rightleftarrows 3O_2$ as an illustration.[11] Two ozone molecules may be represented as in Fig. 8 (*a*); there are bonds linking the nuclei of each molecule, and 'gaps' separating the molecules. In order to rearrange these two ozone molecules into three oxygen molecules, two bonds of each must be stretched, and ultimately be replaced by gaps, the final state being as in Fig. 8 (*c*). Half-way between (*a*) and (*c*) there must be a condition in which the differences between bonds and gaps disappear; this is represented by Fig. 8 (*b*) and is known as the 'transition state' (or 'critical complex'[12]). Since the stretching of the bonds involves the expenditure of work, the transition state is associated with a relatively high energy content. In passing from (*a*) to (*b*) the energy of the system rises, and when the products are formed from the transition state, i.e. as (*b*) passes into (*c*), it falls again. These energy changes are shown diagrammatically in Fig. 9. The minima (*R* and *P*) represent the normal or unexcited states of the reactants and the products respectively, and the crest of the curve (*T*) represents the transition state. The reactants and the products are thus separated by an 'energy barrier' the height of which gives the energy of activation.

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[10] The decomposition of hydrogen iodide by light, in common with many other photochemical processes, occurs by dissociation of a single molecule, HI → H + I.

[11] *J.C.S.* 1937, 629.

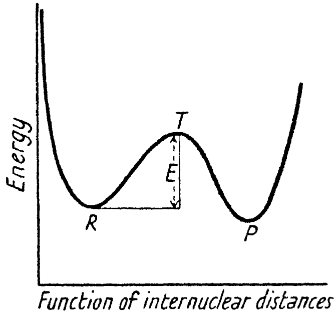

FIG. 9.

A simple substitution reaction, XY+Z = XZ+Y, may be visualized in a similar way.[13] London has shown that, in a bimolecular process of this kind, the attacking reagent Z will approach the molecule XY along the line of the axis of the latter (as illustrated in Fig. 10), and further that Y will recede as Z approaches; the addition of Z and the removal of Y proceed simultaneously.[14] Eyring and Polanyi adopt a three-dimensional representation, in which the co-ordinates are the energy of the system containing X, Y, and Z, and the internuclear distances XY and XZ. This is conveniently depicted on a 'contour diagram' constructed by drawing lines of constant energy upon the plot of XY against XZ, as shown in Fig. 11. The dotted lines are the 'energy contours', their altitude increasing in three directions from the minima at *R* and *P*. *R* therefore lies at the bottom of a 'valley', which is flanked on either side by 'energy hills' and which runs upwards to an 'energy pass' at *T*, while a similar 'valley' descends to *P*. When Z is at a great distance from XY, the nuclear separation of X and Y is represented by *a*, and the energy of the system has its minimum value. As Z approaches (i.e. XZ decreasing), the distance XY increases, slowly at first, and then more rapidly as shown by the line *RT*. At the same time the energy increases, and the system ascends the 'valley' *RT* to the 'pass' at

[12] Compare Brönsted, *Z. physikal. Chem.* 1922, **102**, 169.

[13] Eyring and Polanyi, ibid. 1931, **12**, 279. Again the process is assumed to be 'adiabatic'.

[14] *Z. Elektrochem.* 1929, **35**, 552. The view is summarized by Polanyi, ref. 8.

T, where it is in its transition state. There is here no distinction between the relationship of X to Y and to Z. As Z approaches still nearer to X, however, Y continues to recede, and the system now descends the valley *TP* until, at *P*, XZ has the value *b*, the normal internuclear separation for the molecule XZ, and Y is outside the sphere of action. The pass at *T* represents the energy barrier between XY and XZ, and its height is a measure of the energy of activation for the process $XY+Z = XZ+Y$. The less simple process of substitution in a 'four-centre system' may be regarded similarly.

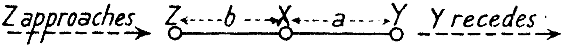

FIG. 10.

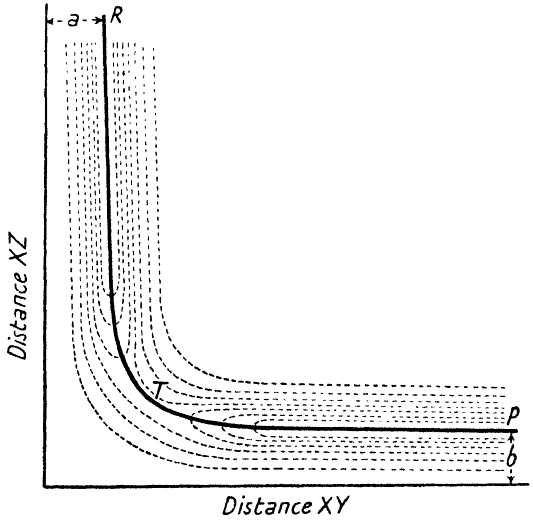

FIG. 11.

Reactions in Solution. The simple collision theory has proved highly successful when applied to gaseous reactions, but attempts to extend the same conceptions to reactions in the liquid phase or in solution are at once met with the difficulty arising from lack of knowledge of the conditions existing in the liquid state. No complete interpretation of the effect of the solvent upon reaction velocity has as yet been reached;[15] it is difficult, moreover, to estimate the extent to which the kinetic theory may be employed in solution, and further complications may arise owing to solvation phenomena, energy transfers due to collisions of solute with solvent molecules, ionization phenomena, and other causes.[16]

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[15] This is sometimes very great. Thus Menschutkin (*Z. physikal. Chem.* 1890, **6**, 41) found the combination of ethyl iodide with triethylamine to be nearly a thousand times as fast in benzyl alcohol as in hexane. Attempts to correlate such effects with physical properties of the solvent are summarized by Moelwyn-Hughes, ref. 18, p. 117,

The earliest comparisons of experimentally determined velocities in solution with those calculated on the basis of the simple collision theory (by the method of Lewis) indicated a large divergence.[17] Nevertheless, a comprehensive survey of the available data by Moelwyn-Hughes revealed the fact that of 181 bimolecular reactions which had been studied in solution with reasonable accuracy, more than 40 per cent. had velocities of the same order of magnitude as those calculated.[18] Further, the decomposition of nitrogen pentoxide, the conversion of *d*-pinene to dipentene (unimolecular reactions), and the decomposition of chlorine monoxide (bimolecular) were found to have approximately the same rates and energies of activation in the gas phase and in certain solvents.[19] Since it was improbable that in a bimolecular process, such as the decomposition of chlorine monoxide, there could be an accurate neutralization of opposing factors which would leave both the velocity and the energy of activation unchanged, it was concluded that the collision frequency of molecules in dilute solution is not very different from that in a gas at the same concentration. A demonstration of the similarity of the two for certain diene syntheses (1 : 4-additions to conjugated olefinic systems) has recently been given by Wassermann.[20]

The velocity coefficient of a reaction may therefore be expressed, with a good degree of approximation, by the general formula

$$k = PZe^{-E/RT}, \tag{2}$$

where E is the energy of activation, Z is the collision frequency, and P is a probability factor which expresses the proportion of the collisions between sufficiently energized molecules which actually lead to the formation of the products of reaction. For the majority of bimolecular reactions in the gaseous phase, P is not far from unity,[21] indicating that activation is not only a necessary but also a sufficient condition for reaction. The investigation of bimolecular reactions in solution, on the other hand, has given values of P which cover a wide range down to 10^{-8}.

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[16] See Hinshelwood, *Kinetics*, p. 248.

[17] Christiansen, *Z. physikal. Chem.* 1924, **113**, 35; Norrish and Smith, *J.C.S.* 1928, 129.

[18] *Kinetics of Reactions in Solution* (Oxford University Press, 1933), chap. iv.

[19] Eyring and Daniels, *J. Amer. Chem. Soc.* 1930, **52**, 1472; Smith, ibid. 1927, **49**, 43; Moelwyn-Hughes and Hinshelwood, *Proc. Roy. Soc.* 1931, **131**, A, 177.

[20] *J.C.S.* 1936, 1028. The value of P for these reactions is about 10^{-6}.

[21] See p. 68.

An alternative treatment of reaction velocities approaches the problem from the standpoint of thermodynamics; this is the 'Transition State Method', employed by Polanyi, Eyring, and others.[22] The collision term PZ is here replaced by the thermodynamic probability of the transition state. Hinshelwood compares the two methods of approach in the following words:

> 'The transition state method and the kinetic method of treating reaction velocity problems are very much more similar than they might appear at first sight. Neither can be said to stand in opposition to the other. The thermodynamic method frequently has the advantage of a greater formal elegance of its equations and a greater generality. On the other hand, this quality is accompanied by the corresponding defect that the magnitudes operated with are often quite inaccessible to experimental control, and further, that the plausibility of certain assumptions cast in a mathematical form is less easy to assess at its face value than it would be with the corresponding assumptions of the alternative method.'[23]
>
> 'It seems, then, that the collision theory is not really at a fundamental disadvantage, if, as a matter of taste, we prefer to approach the problem in that way.'[24]

The kinetic method has the definite advantage that it provides a simple physical picture of the reaction, and it is therefore adopted here.

Hinshelwood and Winkler have enumerated a number of factors which may operate to reduce the probability factor P below unity, and also some factors which may tend to increase P.[25] For a reaction $A+B \rightarrow$ products, taking place in solution, the velocity may be less than that predicted by the kinetic theory for any or all of the following reasons:

(*a*) The colliding molecules must be so oriented that the reactive groups are brought within each other's sphere of influence.

(*b*) The bond to be broken must be sufficiently near the extreme of its amplitude of vibration for rupture to occur (that is, it must be sufficiently weakened).

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[22] Eyring, *J. Chem. Physics*, 1935, **3**, 107; Evans and Polanyi, *Trans. Faraday Soc.* 1935, **31**, 875; Polanyi, ref. 11. See also various contributions to a discussion on Reaction Kinetics, *Trans. Faraday Soc.* Jan. 1938.

[23] *J.C.S.* 1937, 635.

[24] Hinshelwood and Winkler, ref. 25, p. 373.

[25] *J.C.S.* 1936, 371.

(*c*) Access to the reactive centre may be impeded by the neighbouring groups, a collision being effective only when these groups are at that point of their oscillation which opens a sufficiently wide angle for the approach of the reagent.

(*d*) A favourable orientation of solvent molecules may be necessary. Thus if the colliding molecules, as a result of the fulfilment of the necessary energy, phase, and orientation conditions, have actually 'got to grips' and formed the transition complex, the intervention of the molecules of the solvent may be necessary for the consummation of the reaction.[26] In spite of the fulfilment of all the conditions necessary for the production of the *complex*, the collision may not result in the formation of the *products*.

The unfavourable effect of these factors will, however, be lessened by some or all of the following:

(*a*) Simplicity of the reacting molecules.
(*b*) A lengthened duration of collision, the extreme case of which is the formation of a definite addition complex.
(*c*) Ionic charges on the reacting molecules; it is worthy of note that reactions which proceed at normal rates in solution ($P = 1$) usually involve an ion.
(*d*) Specific kinds of energy transfer, which will cause the substances to behave as simpler structures.

The combination of factors such as those listed above would account for values of P extending over several powers of 10.

The Influence of Substituents. Since the velocity of a chemical change can be represented by the formula $k = PZe^{-E/RT}$, and the collision frequency Z varies but little from one reaction to another (it is always about $2{\cdot}8 \times 10^{11}$), it is evident that the marked effects of constitutional changes such as the introduction of highly polar substituents may be due to differences in E, in P, or in both. For several reactions of nuclear-substituted benzene derivatives it has been shown that the influence of the substituents upon the velocity (groups in the *o*-position being excluded) is to be ascribed almost entirely to changes in the energy of activation. The examples for which this has been demonstrated include (I) the chlorination of phenolic ethers,[27] (II) the benzoylation of anilines,[28] (III) the alkaline hydrolysis of benzoic esters,[29] (IV) the reaction of methyl iodide with dimethylanilines.[30]

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[26] Perhaps to remove energy from the complex; Hinshelwood, *Trans. Faraday Soc.* **1936, 32,** 970.

From the equation $k = PZe^{-E/RT}$ it follows that

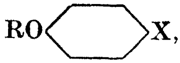
$$\log_e k = \log_e P + \log_e Z - E/RT,$$

or, since changes in Z may be ignored, $\log_e k = \text{const.} + \log_e P - E/RT$. For a definite value of P, therefore,

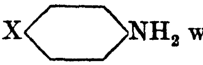
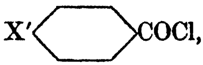
$$\log_e k = \text{const.} - E/RT \qquad (3)$$

and the plot of E against $\log_e k$ for any given temperature is a straight line having the slope $-RT$ (or $-2{\cdot}303RT$ if $\log_{10} k$ is plotted).[31] Figs. 12, 13, 14, and 22 (p. 251) show this plot for the reactions referred to above; in each case the energies of activation for a series of nuclear-substituted derivatives were determined from the temperature coefficients of the velocities, and in the figures these values are plotted against the logarithms of the velocity coefficients for one temperature. The straight lines have the theoretical slope $-2{\cdot}303RT$.

The reactions concerned are:

I. Chlorination of ,

where R = CH_3, C_2H_5, $CH(CH_3)_2$, C_5H_{11}, CH_2COOH, $CH_2C_6H_5$ or substituted $CH_2C_6H_5$
and X = NO_2, F, Cl, COC_6H_5 or COC_6H_4Cl.

II. Reaction of  with ,

where X and X′ = H, CH_3, Cl, or NO_2.

III. Alkaline hydrolysis of (*m* or *p*) $X{\cdot}C_6H_4{\cdot}COOC_2H_5$,
where X = H, NH_2, OCH_3, CH_3, Hal, or NO_2.

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[27] Bradfield and B. Jones, *J.C.S.* 1928, 1006, 3073; Bradfield, W. O, Jones, and Spencer, ibid. 1931, 2907; Bradfield, *Chem. and Ind.* 1932, **51**, 254; Jones, *J.C.S.* 1942, 418.

[28] Williams and Hinshelwood, ibid. 1934, 1079.

[29] Ingold and Nathan, ibid. 1936, 222. Evans, Gordon, and Watson, ibid. 1937, 1430.

[30] Laidler, ibid. 1938, 1786. Evans, Watson, and Williams, ibid. 1939, 1345.

[31] The value of *P* determines the *position* of the line; this is the principle adopted by Hinshelwood and Winkler (see ref. 25) in their diagram illustrating the distribution of *P* values over a range extending from unity to 10^{-8}.

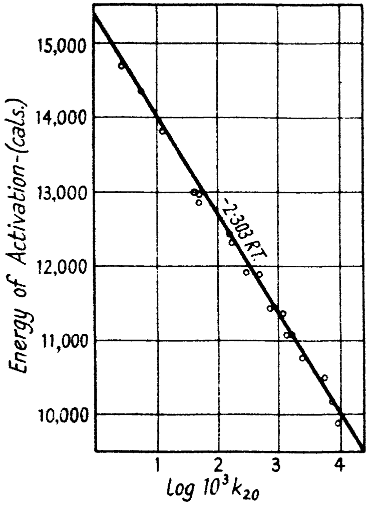

Fig. 12. Reaction I. Chlorination of phenolic ethers $RO \cdot C_6H_4 \cdot X$ (B. Jones, *J.C.S.* 1942, 418).

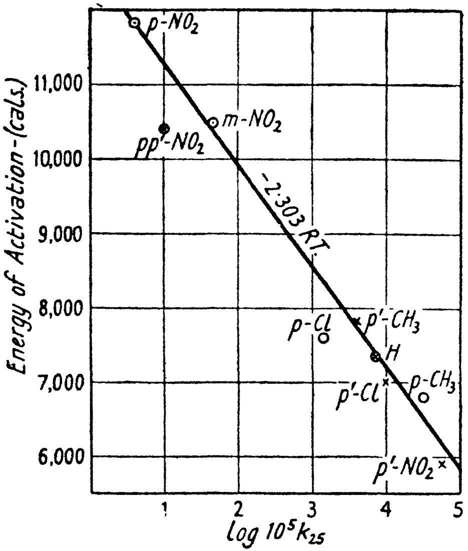

Fig. 13. Reaction II. Benzoylation of anilines (Williams and Hinshelwood).

⊙ = Substituent in amine.
× = Substituent in acid chloride.

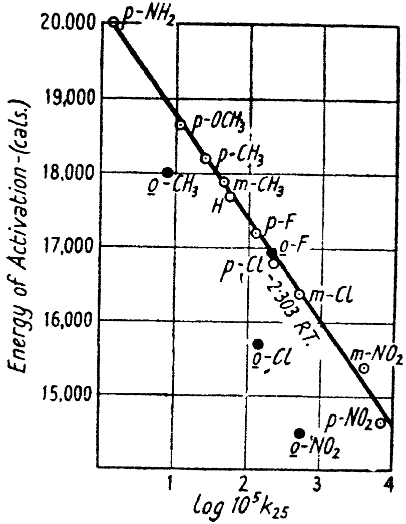

Fig. 14. Reaction III. Alkaline hydrolysis of substituted ethyl benzoates (Ingold and Nathan; Evans, Gordon, and Watson).

IV. Addition of CH_3I to (*m* or *p*) $X \cdot C_6H_4 \cdot N(CH_3)_2$,
where X = H, OCH_3, CH_3, OC_6H_5, C_6H_5, or Hal.

The order of magnitude of the factor P is 10^{-5} for reaction I, 10^{-7} for reaction II, 10^{-2} for reaction III, and 10^{-4} for reaction IV.

An inspection of figures 12, 13, 14, and 22 (page 251) makes it clear that in all the four reactions the plot of $\log k$ against E for the different compounds studied, with the exception of those having substituents in the *ortho*-position (which are discussed in Chapter XV), approximates very closely to a straight line having the theoretical slope of $-2{\cdot}303RT$. The inference is that the electronic displacements caused by substituents in the *m*- and *p*-positions have a very marked influence upon the energy of activation, but only a small effect (if any) upon the probability factor P. The approximate constancy of P is not observed, however, for substituents in the *o*-position.

The results of Bradfield and Jones have shown further that the groups contribute independently and additively to the energy of activation, which may therefore be represented as the sum of a series of terms,

$$E = E_0 + e_1 + e_2 + \ldots,$$

where E_0 is the value relating to the unsubstituted compound, and e_1, e_2, etc., are the contributions (which may be either positive or negative) due to the substituents.

It is probably safe to conclude that, for a given chemical process, the factor P usually retains a very nearly constant value when the reacting substances are *similarly constituted* compounds in which the variable group is *separated from the point of reaction* by a system (e.g. the benzene nucleus) which transmits the electronic displacements set up by the substituents. Under these conditions the effect of the substituent consists essentially in a change in the energy of activation; the value of E is raised or lowered according to the nature of the reaction and of the group. There are some instances, however, in which substituents in the *m*- or *p*-position cause appreciable changes in the probability factor P. The most notable are the acid hydrolysis of ethyl benzoates,[2] the alcoholysis of benzoyl chlorides,[32] and the hydrolysis of arylsulphuric acids;[33] P here increases or decreases with E, but the effect of the change in P is never powerful enough to outweigh the variation of the energy of activation. The acid hydrolysis of the chlorinated acetic esters, which was referred to at the commencement of this chapter, provides an example of the simultaneous variations in E and P where the one effect almost annuls the other, giving only small changes in the velocity.

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[32] Branch and Nixon, *J. Amer. Chem. Soc.* 1936, 58, 2499.

[33] Burkhardt, Horrex, and Jenkins, *J.C.S.* 1936, 1649.

When the variable group is in close proximity to the point of reaction, and local disturbances may therefore contribute to the total effect, simultaneous variations in E and P usually occur. This has been shown in Hinshelwood and Legard's investigation of the kinetics of fifteen esterification reactions involving six different acids (acetic, benzoic, *o*-nitrobenzoic, diphenylacetic, 2 : 4 : 6-trimethylbenzoic and trichloroacetic) and four alcohols (methyl, *iso*propyl, *tert*-butyl, and benzyl), and in Winkler and Hinshelwood's study of twelve reactions of alkyl halides (methyl, ethyl, *n*-propyl, and *iso*propyl) with tertiary bases (trimethylamine, triethylamine, pyridine, and quinoline). The differences in velocity are still due to a great extent to changes in E, but the P factor also varies appreciably.[34] The retardation of reactions by groups in the *o*-position appears to be due sometimes to large increases in the energy of activation (accompanied by a *rise* in P) and at other times to a *decrease* in P with negligible change of E. These effects are discussed in Chapter XV.

The energy of activation and the P factor rise or fall simultaneously with changes in the medium or the pressure. In a catalysed reaction, P is very considerably greater for a charged catalyst than for an uncharged catalyst.[35]

Hughes, Ingold, and Shapiro have pointed out that caution should be exercised before significance is attached to *small* differences in the values of E and P, since the accuracy with which these quantities can be determined is subject to some uncertainty.[36] Thus, in certain reactions there are indications of an appreciable variation with temperature in both the E and P terms of the Arrhenius equation. La Mer and Miller find, for example, that in the dealdolization of diacetone alcohol E increases by nearly 1,400 calories when the temperature is raised from 5° to 32·5°, and then decreases by 500 calories on a further rise of temperature to 45°; P shows a parallel variation.[37] Similar phenomena have been observed in certain other reactions, although, as La Mer says, 'the temperature variation of E is frequently within the limits of experimental error'; it must be pointed out, indeed, that large variations may be due to some change in the mechanism of the reaction. Evans and Jenkins[38] have recently pointed out that the variation of the dielectric constant of the medium with temperature is likely to introduce an error into the value of the energy of activation determined in the usual way, viz. from the slope of the line connecting $\log k$ with $1/T$. All these considerations make it clear that it is unsafe to attach importance to *small* variations in E or P. Nevertheless, in those cases (which are numerous) where *large* variations of these parameters are found, valuable results have been obtained by the application of this modern kinetic method to problems concerning the reactions of organic compounds. Examples are to be found in later chapters.

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[34] *J.C.S.* 1935, 587, 1147.

[35] Hinshelwood, *Trans. Faraday Soc.* 1938, **34**, 138.

[36] *J.C.S.* 1936, 228.

[37] *J. Amer. Chem. Soc.* 1935, **57**, 2674. This is, of course, a case where the variations are unusually large.

Finally, reference must be made to certain relationships which have been traced between energies of activation and free energies of ionization. The variations in reactivity which result from the introduction of substituents into the *m*- or *p*-positions of an aromatic compound are usually due to changes in the energy of activation; the changes in $\log k$ are therefore a measure of the changes in E. Similarly, the variations in $\log K$ in a series of carboxylic acids are a measure of changes in the free energy of ionization. Hammett[39] has plotted the values of $\log k$ for a given reaction of a series of aromatic compounds (e.g. the hydrolysis of *m*- and *p*-substituted ethyl benzoates) against the values of $\log K$ for the corresponding series of acids, and he finds an approximately linear relationship. The plot of the $\log k$ values for one reaction against those for another is also linear. Writing ΔE_1 and ΔE_2 for the energy changes due to a given substituent in the two processes, the relationship becomes $\Delta E_1 = \alpha \Delta E_2$; this means that, for different substituents, a constant fraction of the effect is transmitted through a given structure.[40] Hammett therefore expresses the effect of a group upon the velocity of a given reaction as $\Delta \log k = \sigma\rho$, where σ is a 'substituent constant' determined by the nature of the group, and ρ is a 'reaction constant' dependent upon the reaction and the external conditions. The linear relationship breaks down in cases where the factors which can operate in the processes are not the same.[41] The relationship between the $\log K$ values for *m*-substituted benzoic acids and the dipole moments of the corresponding substituted benzenes has a parallel in the expression $E = E_0 \pm c(\mu + a\mu^2)$ for the effects of *m*-substituents upon the energy of activation of a reaction; the variation of mesomeric moments and the existence of time-variable effects render the relationship inapplicable to *p*-substituted compounds.[42]

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[38] *Trans. Faraday Soc.* 1940, **36**, 818.

[39] *J. Amer. Chem. Soc.* 1933, **55**, 4079; 1937, **59**, 96. *Chem. Reviews*, 1935, **17**, 125. *Trans. Faraday Soc.* 1938, **34**, 186. Compare Burkhardt, Ford, and Singleton, *J.C.S.* 1936, 20.

[40] Hinshelwood, *J.C.S.* 1937, 640; *Trans. Faraday Soc.* 1938, 34, 172.

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[41] Dippy and Watson, *J.C.S.* 1936, 436.

[42] Watson, *Trans. Faraday Soc.* 1938, **34**, 165.

VI

APPLICATIONS OF THE ELECTRONIC THEORY IN ORGANIC CHEMISTRY. GENERAL DISCUSSION[1]

THE observations described in the preceding chapters lead inevitably to the conclusion that, relatively to hydrogen the standard of reference, atoms and groups may either repel or attract electrons. This is clearly demonstrated, for example, by the values of the molecular electric moments of organic compounds, by the strengths of acids, bases, and phenols, and by the known facts concerning a large variety of chemical reactions. The effect of this repulsion or attraction of electrons (Flürscheim's 'polar factor') is relayed by induction along a chain of atoms ('inductive effect') and also transmitted through space or the medium ('direct' or 'field' effect), as first visualized by G. N. Lewis in 1916. In either case it diminishes with increasing distance from the source. It is not possible to determine the proportion which is transmitted by either route, and Ingold's term 'inductive effect' is almost invariably employed to denote the whole effect, irrespective of the mode of propagation. It is conventional to represent repulsion and attraction of electrons by positive and negative signs respectively; thus the effect of the group X in $X \rightarrow C$ is designated $+I$, and that of Y in $Y \leftarrow C$ is written $-I$.[2] The most powerful of all inductive effects are those of atoms with which an integral charge is associated, such as nitrogen in a quaternary ammonium salt or oxygen in the phenoxide ion. It must be emphasized that the inductive effect does not involve covalency changes. The electrons do not lose contact with one nucleus, nor do they come under the influence of another; the covalent pair may be regarded as simply drawn nearer to one nucleus, the octets remaining intact. Moreover, the effect represents a *permanent* condition of the molecule, measurable in the electric moment.

Numerous observations have shown, however, that the influence of a group cannot always be expressed completely in terms of its inductive effect. In the preceding chapters, reference has been made to various indications of the operation of other factors which are distinct from the inductive effect and, since they may even differ from it in sign, must have a different mechanism. Long before the advent of the electronic theory of valency, indeed, the necessity for postulating at least *two* independent factors was pointed out by Vorländer,[3] who suggested that the influence of a group is dependent both upon its polar character and upon its 'state of saturation'.

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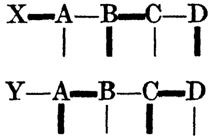
[1] See Ingold, *Chem. Reviews*, 1934, **15**, 225; Robinson, *Outline of an Electrochemical Theory of the Course of Organic Reactions* (Institute of Chemistry, 1932); *J. Soc. Dyers and Colourists, Jubilee Issue*, 1934, p. 65.

[2] But see p. 31, footnote 32.

The Theories of Alternating Affinities and Alternating Polarities. In the early years of this century, theoretical organic chemistry was influenced very powerfully by the contrast which appeared to exist, in benzene derivatives, between the *ortho* and *para* (2,4,6) positions on the one hand and the *meta* (3,5) positions on the other; great significance was attached to the fact that substitution occurs mainly *either* at the *o*- and *p*-carbon atoms *or* at the *m*-carbon atom. This led to the assumption of an alternation either in the 'affinity contents' of bonds or in the polarities of the carbon atoms of the benzene nucleus (and also, indeed, of a saturated chain). The theory of alternating affinities was used with considerable success by Flürscheim (1902 and later).[4] Adopting the views of Werner, he regarded each atom as being endowed with a definite amount of available affinity; when combination occurred, other atoms claimed varying proportions of this affinity, which was thus utilized to a large extent in forming bonds ('bound affinity'). Some 'residual' or 'free' affinity remained, however, and the reactivity of the combined atom was dependent upon this. These postulates led to the conceptions of alternate bonds of high and low affinity ('strong' and 'weak' bonds) and alternate atoms of high and low residual affinity. This is illustrated in the formulae below, where large and small amounts of affinity are represented by thick and thin lines respectively.



The atom X, having a high 'affinity demand' (i.e. greater than that of hydrogen), forms a 'strong' bond with A (thick line); the available affinity of A is thus largely utilized in forming the bond, leaving a relatively small amount for the link with B and also a small amount of residual affinity on A (thin lines). B, having used only a small proportion of its affinity in the bond with A, has a high residual affinity and also forms a 'strong' bond with C (thick lines), and so on. The atom Y, on the other hand, has a low affinity demand (less than that of hydrogen), and hence the state of affairs is completely reversed. The effect of this distribution of affinity is termed by Flürscheim the 'quantitative factor', and is regarded as being superimposed upon the 'polar factor'.[5] The following are examples of Flürscheim's use of these conceptions. The fact that *p*-hydroxybenzoic acid is *weaker* than the unsubstituted acid, while its *m*-isomeride is *stronger*, is ascribed to a high affinity demand on the part of hydroxyl, leading to the alternations

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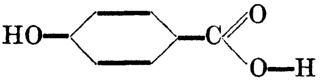
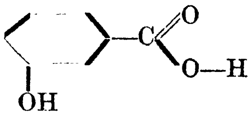
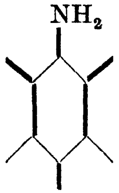
[3] *Annalen*, 1902, **320**, 110.

[4] See *J.C.S.* 1909, **95**, 718; *Chem. and Ind.* 1925, **44**, 246, and references there cited.

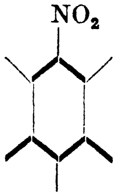




In the *m*-substituted acid the quantitative factor reinforces the polar factor, leading to a stronger acid, while in the *p*-acid it operates against the polar factor and is strong enough to overcome it. Directive influences in aromatic substitution were also ascribed to the varying affinity demands of substituents; a demand greater than that of hydrogen leads to the development of free affinity at the *o*- and *p*-positions, where substitution therefore occurs, while conversely a demand less than that of hydrogen leads to *m*-substitution. This is illustrated below.



(*op*-substitution)



(*m*-substitution)

The rival theory postulated the development of positive and negative charges, perhaps permanently, or perhaps at the moment of reaction, on alternate carbon atoms. The theories of Fry[6] and Vorländer[7] were of this type. The alternate polarity view was adopted by Lapworth,[8] who regarded the alternations as being induced by a 'key-atom', and requiring, for their full development, a system of alternate single and double bonds. Lapworth based his theory on arguments such as the following. The addition reactions of the carbonyl group (e.g. cyanohydrin formation) lead to the representation $>\overset{\oplus}{C}=\overset{\ominus}{O}$; this refers to the behaviour of the group at the instant of reaction, and permanent polarization is not postulated. The aldol reaction, in which >CH—CO—, for example, takes the place of HCN in cyanohydrin formation, indicates that the hydrogen of this group is positive with respect to the α-carbon, and hence the representation is extended to $\overset{\oplus}{H}-\underset{\wedge}{\overset{\ominus}{C}}-\underset{|}{\overset{\oplus}{C}}=\overset{\ominus}{O}$, which is confirmed by the reaction $>\overset{\oplus}{C}=\underset{|}{\overset{\ominus}{C}}-\underset{|}{\overset{\oplus}{C}}=\overset{\ominus}{O}+HCN = >C(CN)-\underset{|}{C}H-\underset{|}{C}=O$.[9] The resemblance of the γ-hydrogen of ethyl crotonate to the α-hydrogen of ketones[10] leads to the further extension

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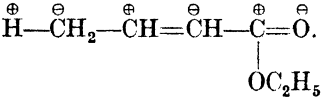
[5] See Chap. II, p. 29.

[6] *The Electronic Conception of Valence* (Longmans, 1921).

[7] *Ber.* 1919, **52**, 263; 1925, **58**, 1898.



$$\overset{\oplus}{H}-\overset{\ominus}{CH_2}-\overset{\oplus}{CH}=\overset{\ominus}{CH}-\underset{\displaystyle |\atop OC_2H_5}{\overset{\oplus}{C}}=\overset{\ominus}{O}.$$

These alternations are regarded as having their origin in the effect of the doubly linked oxygen, which is the 'key-atom'. It is clear that the alternate polarity and alternating affinity views, though based upon different premises, led to much the same interpretation of the processes of organic chemistry.

The expressions 'state of saturation' (Vorländer), 'affinity demand' (Flürscheim), and 'key-atom' (Lapworth) are capable of interpretation in terms of the electronic theory of valency, and the modern standpoint has been reached through the development, on electronic lines, of certain features of the older views, in conjunction first with Lowry's postulate of electromeric displacements and later with the conception of quantum-mechanical resonance. Just as Flürscheim's 'quantitative factor' and Lapworth's 'alternate polarity' were regarded as effects additional to or superimposed upon a 'polar factor' (Flürscheim) or 'general polarity' (Lapworth), so the 'electromeric' and 'mesomeric' effects of present theory represent influences which do not exclude but may operate in conjunction with or in opposition to the inductive effect.[11]

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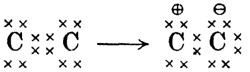
[8] *Mem. Manchester Phil. Soc.* 1920, **64**, No. 3; *J.C.S.* 1922, **121**, 416. Compare Kermack and Robinson, ibid., p. 427.

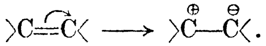
[9] Further reference to this reaction is made in Chap. XI.

[10] Lapworth, *J.C.S.* 1901, **79**, 1273.

Electromeric Displacements. In 1923 Lowry ascribed the reactivity of double linkages to a type of polarization in which a pair of electrons from the double bond becomes the sole property of one atom.[12] In the case of the olefinic bond this may be represented as follows:

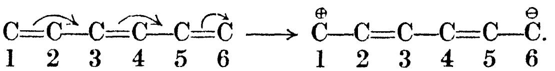


Such displacements, in which 'electrons whilst remaining in one octet enter or leave another',[13] are termed 'electromeric', and are denoted by a curved arrow, thus:



$$>C{=}C< \longrightarrow >\overset{\oplus}{C}{-}\overset{\ominus}{C}<.$$

This distinguishes them from those drifts of electrons without co-valency changes which constitute the inductive effect, and which are represented by straight arrows. Electromeric displacements may proceed along the full length of a chain of atoms linked by alternate single and double bonds:



$$\underset{1}{C}{=}\underset{2}{C}{-}\underset{3}{C}{=}\underset{4}{C}{-}\underset{5}{C}{=}\underset{6}{C} \longrightarrow \underset{1}{\overset{\oplus}{C}}{-}\underset{2}{C}{=}\underset{3}{C}{-}\underset{4}{C}{=}\underset{5}{C}{-}\underset{6}{\overset{\ominus}{C}}.$$

The arrows here indicate that a pair of electrons from the C_1C_2 double bond is released by C_1 and comes under the control of C_3, a double bond between C_2 and C_3 thus being formed; the normal covalency of C_3 is restored by the release of a pair from the C_3C_4 bond; this leads to a double linkage between C_4 and C_5, and finally two electrons from the C_5C_6 double bond become the sole property of C_6. A series of *incomplete* electronic migrations of this kind may be regarded as the electronic analogue of Thiele's conception of 'conjugation'. It is evident that such migrations can occur only in suitable systems such as a chain of alternate single and double bonds or the benzene ring (these are commonly referred to as 'conjugate' systems); a chain of saturated carbon atoms would be disrupted by a similar process.

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[11] The necessity for postulating two factors of a *polar* character appears to have first been stated by Kermack and Robinson (*J.C.S.* 1922, **121**, 430) and by Lapworth and Shoesmith (ibid., p. 1391).

[12] *J.C.S.* 1923, **123**, 822.

[13] Ingold, *Rec. trav. chim.* 1929, **48**, 798.

This electronic conception of conjugation was very soon incorporated in the theory of aromatic substitution and allied processes, and in 1926 the application of the electronic theory of valency to aromatic systems was the subject of two comprehensive papers, the first by Allan, Oxford, Robinson, and Smith,[14] and the second by Ingold and Ingold.[15] Electromeric displacements of the type postulated by Lowry were at first regarded as occurring only at the demand of a reagent, but it then became evident that they must often be to some extent permanent. This conclusion was reached largely on the basis of dipole moment values,[16] and confirmatory evidence was found in observations both of equilibria (e.g. the dissociation constants of acids), which are not influenced by time-variable factors since they depend upon a comparison of two ground (i.e. unexcited or normal) states, and of reactions, which can be accelerated but not retarded by a factor which operates only at the demand of a reagent. Finally, the permanent effect was recognized as an instance of quantum-mechanical resonance or mesomerism.[17]

The Mesomeric Effect. One of the most striking features of aromatic substitution is the powerful *op*-directive influence of certain groups which, judging from their effects upon the strengths of saturated aliphatic acids, would be described as electron-attractive (—I). Hydroxyl and groups —OR derived from it are prominent examples. The amino, alkylamino, and dialkylamino groups come into this category, although their influence upon acid dissociation cannot be determined since amino-acids are amphoteric electrolytes. Such groups have one characteristic in common, viz. the atom which is adjacent to the nucleus possesses unshared electrons. If one of these pairs were to enter the bond which links this atom with nuclear carbon, and the normal covalence of the latter were restored by further electromeric displacements in the nucleus, an alternative dipolar structure of a quinonoid type would be formed.[18] This is particularly significant in the case of phenols and anilines (and their derivatives), since compounds having oxygen or nitrogen doubly linked to nuclear carbon (quinones, quinone-imines) are well known.

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[14] *J.C.S.* 1926, 401. See also earlier papers by Sir Robert Robinson, ibid. 1925, **127**, 1618, and *Chem. and Ind.* 1925, **44**, 456.

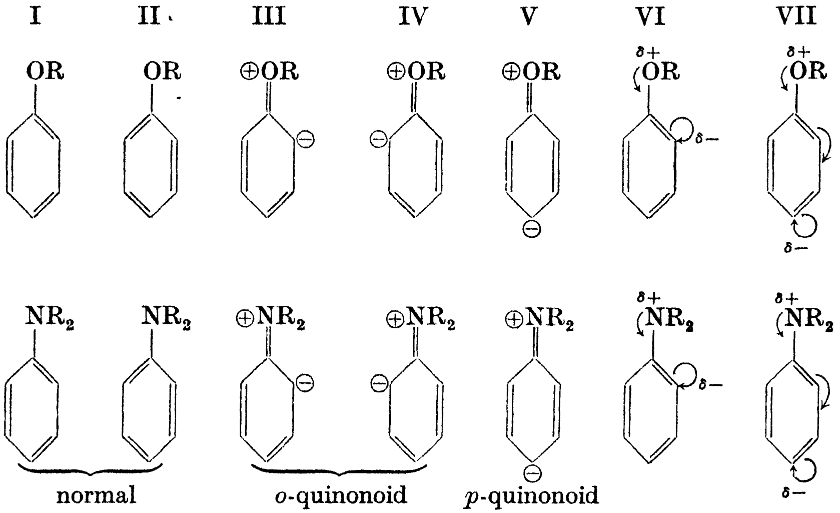
[15] *J.C.S.* 1926, 1310.

[16] See Chap. IV, p. 59.

[17] Ingold, *J.C.S.* 1933, 1120.

[18] The whole process would, of course, be impossible if the group were attached to a saturated system.

The benzenoid and quinonoid structures, in fact, have all the characters necessary for resonance, and all the structures I to V (below) participate in the mesomeric state. In other words, the group, by increasing its covalency with nuclear carbon, sets up permanent (though incomplete) electromeric displacements as represented in VI and VII. Ingold speaks of this as the Mesomeric Effect (+M). Evidence for the existence of such a permanent effect is found in the different values of the dipole moments of aromatic compounds and their aliphatic analogues; it is this effect which gives rise to the 'mesomeric moment' in the former.[16] It is evident that the bond linking the hydroxyl group of phenol, for example, to the nucleus will have, to some extent, the characters of a double bond (owing to the contribution of structures such as III, IV, and V to the mesomeric state); as confirmatory evidence Pauling has found indications of *cis* and *trans* isomerides of *o*-chlorophenol by observations of its infra-red spectrum.[19]



It is clear that the mesomeric effect of a group such as —OR or —NR$_2$ increases the electron-availability at the *o*- and *p*-positions, which acquire a fractional negative charge (indicated by δ— in VI and VII above). These positions will therefore form the points of attack by an electrophilic (electron-seeking) reagent, and hence the groups —OR and —NR_2 are *op*-directive. The mesomeric effect will also facilitate side-chain reactions of Type A,[20] e.g.

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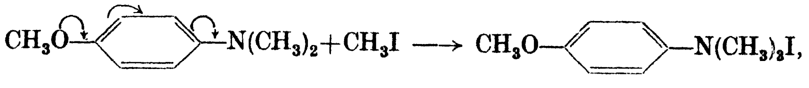
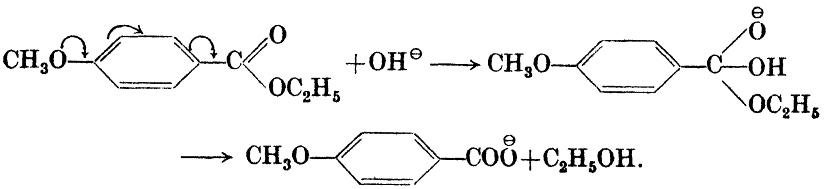
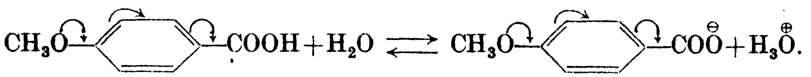
[19] *J. Amer. Chem. Soc.* 1936, **58**, 94.



but will operate against Type B reactions, e.g.



The relatively low dissociation constants of *p*-hydroxybenzoic, *p*-anisic, and analogous acids are accounted for similarly, since the mesomeric effect of the group is unfavourable to dissociation and at the same time promotes recombination of the ions; i.e. it favours the left-hand side of the equilibrium



Since a *m*-quinonoid form is not possible (it would demand the expansion of the covalency of carbon beyond its limit of eight electrons), the mesomeric effect cannot be transmitted to the *m*-position. Thus *m*-OCH_3, for example, influences a reaction in a side-chain in accordance with its rather weak inductive effect (—I); this is illustrated by the facts that *m*-methoxybenzoic acid is *stronger* than benzoic (just as methoxyacetic is stronger than acetic acid), the order of strengths being *m*-$OCH_3 > H >$ *p*-OCH_3,[21] and that the *m*-substituted ester undergoes alkaline hydrolysis rather more quickly than ethyl benzoate does.[22] The effect of the fractional charge at the *ortho*- and *para*-carbon atoms may, however, be feebly relayed to the *m*-position by an inductive mechanism (VIII below), and a similar relay may occur along a saturated side-chain. For example, in *p*-methoxyphenylacetic acid the mesomeric effect of methoxyl cannot be transmitted *as such* to carboxyl through the intervening methylene group; nevertheless *p*-OCH_3 depresses the dissociation constant, a fact which is interpreted diagrammatically in IX below.[21]

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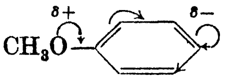
[20] The terms 'Type A' and 'Type B' are explained on p. 41.

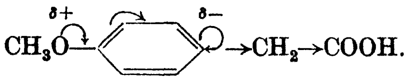
[21] Dippy, Watson, and Williams, *J.C.S.* 1935, 346.

[22] Kindler, *Annalen*, 1926, **450**, 1; 1927, **452**, 90.

VIII

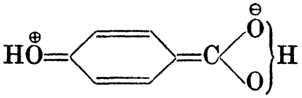


IX

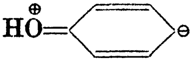


The mesomeric effect of a given group is not constant in magnitude; Bennett and Glasstone have shown this.[23] For instance, the actual (mesomeric) state of *p*-hydroxybenzoic acid may approach the dipolar form X more closely than phenol approaches XI, and the absence of any quantitative relationship between the dissociation constants of *p*-substituted aromatic acids and the dipole moments of the corresponding substituted benzenes may be ascribed to this.

X

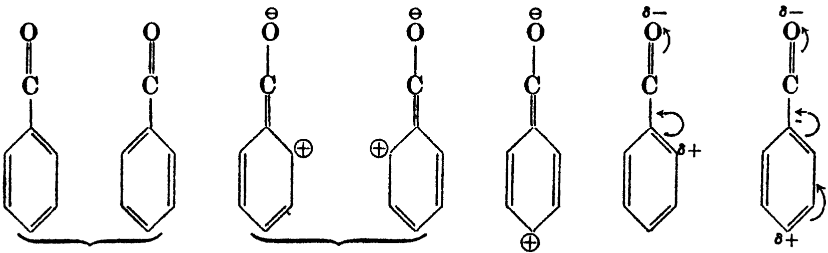


XI



Groups such as $—NO_2$, —COR, —COOH, and —COOR, when linked to the aromatic nucleus, give rise to a state of affairs which is comparable with that produced by —OR and $—NR_2$, but in which the electromeric displacements are in the reverse direction. Thus, a compound $C_6H_5 \cdot COR$ exists normally in a mesomeric state to which all the forms I to V (below) contribute; the effect of the group is equivalent to the initiation of electromeric displacements *towards* itself (VI and VII). This is written −M.

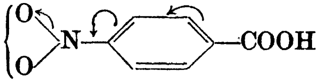
I II III IV V VI VII



This effect thus leads to a *decrease* in electron-availability at the *o*- and *p*-positions. The result is that, as regards the attack of an electrophilic reagent, the *o*- and *p*-positions are selectively deactivated, and therefore substitution occurs at the *m*-position. The

[23] See p. 62.

groups —NO_2, —COR, etc., are therefore *m*-directive. Since these groups also have —I effects, the nucleus is also, to some extent, deactivated as a whole, and *m*-substitution is therefore slow in comparison with *op*-substitution. The latter is due to *activation* of the *o*- and *p*-positions; the former arises through *deactivation* of the whole nucleus and particularly the *o*- and *p*-positions. It is clear that the —M effect will facilitate side-chain reactions of Type B, and retard those of Type A. Like the +M effect, it cannot be transmitted to the *m*-position, and hence *p*-NO_2, for example, influences side-chain processes more powerfully than does *m*-NO_2. Thus, *p*-nitrobenzoic acid is stronger than its *m*-isomeride on account of the process



and the speeds of alkaline hydrolysis of the nitrobenzoic esters stand in the order *p*-NO_2 $>$ *m*-NO_2.[22]

The Electromeric Effect. The inductive and mesomeric effects represent permanent polarizations; they are present in the normal or ground state of the molecule and hence are measured in its dipole moment. Chemical equilibria, such as the ionic equilibria of acids and bases, which depend upon the energies of two ground states, are influenced by the inductive and mesomeric effects. In a reaction a further effect becomes possible, however. Consider again the attack of an electrophilic reagent upon an aromatic molecule C_6H_5OR or $C_6H_5NR_2$, as in nuclear nitration, sulphonation, or halogenation. The molecule is originally in the mesomeric state, between the benzenoid and quinonoid structures, but at the demand of the reagent, and in the highly energized transition complex, the change to the quinonoid form, with its full charge at the *o*- or *p*-position, can be completed. The group may thus give rise momentarily to a far more powerful activating effect than that represented by its mesomeric effect. The very strong activation of the *o*- and *p*-positions by —OR and —NR_2 must be ascribed to the total polarization which occurs as a result of the co-operation of the permanent and time-variable effects. The time-variable factor operates by the same mechanism as the mesomeric effect, but only at the demand of an attacking reagent; its magnitude may therefore vary from reaction to reaction. It is a polarizability effect and not a permanent polarization. The name Electromeric Effect (+E) is given to this, and the sum of the two effects (M+E) is designated the Tautomeric Effect (+T) since similar electronic migrations are involved in a tautomeric change such as $\mathrm{CH_2{=}\overset{\curvearrowright}{CH}{-}CH_2{-}COOH \rightarrow CH_3{-}CH{=}CH{-}COOH}$. The transmission of both effects will clearly be subject to the same limitation, a 'conjugated' system being necessary. Similarly, the —M effect of a group such as $—NO_2$ or —COR can develop into a —E effect (the sum of —M and —E being denoted —T) at the demand of a reagent which seeks a deficiency of electrons; this will not occur in aromatic substitution by an electrophilic reagent, however, for the E effect does not operate against a reaction. In general, the mesomeric effect (+M or —M) can facilitate or retard a reaction; the electromeric effect (+E or —E) can only facilitate, and under other circumstances is inoperative.

Ingold visualizes, in addition to the above polar effects, a time-variable factor, the Inductomeric Effect, which operates by an inductive mechanism. He summarizes the possible polar influences of groups as follows:[24]

	Electrical classification	
Electronic mechanism	*Polarization*	*Polarizability*
General inductive ($\rightarrow$) (I)	Inductive	Inductomeric
Tautomeric ($\curvearrowright$) (T)	Mesomeric (M)	Electromeric (E)

Alkyl Groups. The dipole moments of all saturated aliphatic hydrocarbons are zero, whether the molecule is symmetrical or otherwise; since they are all derived from methane by successive replacements of hydrogen by $—CH_3$, it follows that such replacement does not confer polar characters upon the hydrocarbon molecule. Similarly, the moments of aliphatic alcohols, ketones, and nitro-compounds are almost constant throughout the homologous series. In the aliphatic nitriles the moments are practically constant after the second member (propionitrile). In alphyl chlorides there is an increase up to the *n*-propyl compound, but the iodides show a larger increase and the limiting value is not reached at *n*-butyl iodide; for bromides the moments increase more than for chlorides but less than for iodides. The following table records the values of the dipole moments of the earlier members of several homologous series of aliphatic compounds RX; they are the mean results of concordant measurements on vapours, as given by Groves and Sugden.[25] Values for R = H are also included.

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[24] *Chem. Reviews*, 1934, **15**, 233.

Dipole Moments of Aliphatic Compounds RX

X =	Cl	Br	I	CN	NO_2	OH
R = H	1·03	0·78	0·38	2·93	..	1·84
R = CH_3	1·87	1·80	1·64	3·94	3·54	1·69
R = C_2H_5	2·05	2·01	1·87	4·04	3·58	1·69
R = *n*-C_3H_7	2·10	2·13	2·01	4·05	3·57	1·65
R = *n*-C_4H_9	2·11	2·15	2·08	4·09	3·55	1·65
R = *iso*-C_3H_7	2·15	2·19	..	..	..	1·63

The values, viewed as a whole, appear to indicate that alphyl groups have a rather feeble capacity for electron release, which increases with the size of the group up to a limit which is imperfectly defined and which varies with the attached group.[26] The sequence $CH_3 < CH_3 \cdot CH_2 < (CH_3)_2CH$ for alkyl chlorides and bromides, where hydrogen atoms are progressively replaced by methyl groups, also leads to the conclusion that methyl is electron-repulsive. A similar electron-repulsion is indicated by the dissociation constants of the lower saturated aliphatic acids (below).

Acid	$10^5 K_{\text{class}}$
$H \cdot COOH$	21·4
$CH_3 \cdot COOH$	1·82
$CH_3 \cdot CH_2 \cdot COOH$	1·34
$(CH_3)_3C \cdot COOH$	0·98

The influence of methyl upon the reactions of aliphatic compounds is illustrated in the hydrolyses of alphyl halides, to which reference is made later;[27] electron-repulsion is again indicated. Among aromatic and unsaturated compounds, examples of the electron-repulsive characters of alphyl groups are found in their *op*-directive power and their influence upon side-chain reactions, the dipole moments of the alkylbenzenes, the lower dissociation constants of *m*- and *p*-toluic acids than of benzoic acid, and the facilitation of the addition of bromine to ethylene by substituent alkyl groups.[28]

The capacity of alphyl groups to repel electrons cannot be doubted, therefore. It must involve an inductive mechanism, since it is observed when the group is attached to a saturated chain; also, unshared electrons such as are possessed by hydroxyl are not here available for the initiation of electromeric displacements. In order to explain the absence of an electric moment in aliphatic hydrocarbons, Ingold suggests that this effect is not an intrinsic property of the bond linking the alphyl group to the remainder of the molecule, but that

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[25] *J.C.S.* 1937, 158.

[26] In all homologous series, hydrocarbons excepted, the increments in the heat of formation for successive additions of CH_2 grow larger as the series is ascended. See Sidgwick, *The Covalent Link in Chemistry* (Cornell University Press, New York, 1933), p. 115.

[27] See Chap. X.

[28] These are all referred to elsewhere.

> 'alkyl groups will merely exert those polar effects which are impressed on them by the other groups present in the molecule. The important property of alkyl groups is that they are more *polarizable* than hydrogen, and thus —CH_3, although non-polar when CH_3—CH_3 is compared with H—CH_3, becomes an electron-repelling group when the comparison is between CH_3—COOH and H—COOH or between CH_3—CH_2Cl and H—CH_2Cl. Since the majority of substituents commonly encountered are attractors of electrons, alkyl groups generally function as feebly electron-repelling groups.'[29]

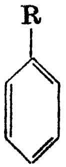
A powerful inductive effect such as that of —NO_2 or —COOH is not influenced perceptibly by the environment in which the group finds itself, but when a group is intrinsically almost neutral the environment must be supposed to have an appreciable influence. The electron-repulsive effect (+I) of an alkyl group is therefore detectable only when neighbouring atoms or groups are such as to stimulate its operation.

When an alphyl group is linked to an olefinic or conjugate system, the resonance of the system is directed in accordance with the scheme

$$\mathrm{R{\rightarrow}CH\overset{\curvearrowright}{=}CH_2} \quad \text{or} \quad \mathrm{R{\rightarrow}C\overset{\curvearrowright}{=}C\overset{\curvearrowright}{-}C\overset{\curvearrowright}{=}C\overset{\curvearrowright}{-}C\overset{\curvearrowright}{=}C.}$$

The inductive effect of R is stimulated here by the electron-attraction of the unsaturated system, whatever be the origin of the latter (see p. 99). Similarly, in an alkylbenzene the unperturbed structures will include III, IV, and V (below) in addition to I and II; in other words, the alkyl group sets up the electromeric displacements represented in VI and VII.

I



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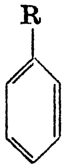

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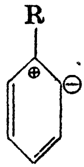

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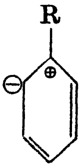

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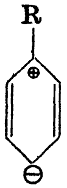
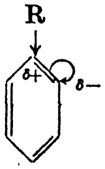
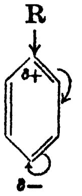


VI



VII



It must be emphasized that this effect is different in its origin from the mesomeric effect of groups such as —OR and —NR_2. It does not depend upon an increase in the electron-content of the bond linking the group to nuclear carbon, for alkyl groups have no unshared electrons; it results, nevertheless, in an increased electron-availability at the *o*- and *p*-positions. This leads to activation of these positions towards an electrophilic reagent, with consequent *op* substitution. A further consequence is that alkyl groups influence side-chain processes more powerfully from the *p*- than from the *m*-position. Examples are found in the lower dissociation constant of *p*-toluic than of *m*-toluic acid,[30] and the relative speeds of hydrolysis of the corresponding esters, that of the *p*-isomeride being the slower.[22] The complete effect is, of course, permanent, and therefore included in the dipole moment of an alkylbenzene.

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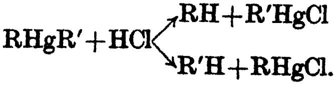
[29] *Chem. Reviews*, 1934, 15, 238.

Since the higher alkyl groups are all derived from the lower by successive replacements of H by CH_3, the electron-repulsive characters of the group should increase in magnitude as the *normal* series is ascended (methyl < ethyl < *n*-propyl, etc.), and also in series such as methyl < ethyl < *iso*propyl < *tert*-butyl. In the *normal* series the differences between successive groups should become smaller as the length of the chain increases, for the point of replacement of H by CH_3 recedes from the point of reaction. This is found in the dipole moments of the homologous alkyl halides and other compounds (see above) which increase gradually to a constant value which is reached quite early in the series (e.g. at *n*-Pr for chlorides and bromides). Similarly, if the alkyl group as a whole is removed some distance from the seat of reaction, as, for example, by interposing an aromatic nucleus, the differences between successive alkyl groups become very small and not easy to detect; this constitutes one of the difficulties which has been encountered in the study of the relative influences of alkyl groups.

The theoretical order of the inductive effects of alkyl groups has been observed in a number of reactions. A notable instance is found in the results of Kharasch and Flenner's comparison of groups extending from methyl to *n*-heptyl,[31] by a method in which they examined the products of decomposition by hydrogen chloride of unsymmetrical mercury dialkyls, RHgR′. Two reactions may occur:



$$\mathrm{RHgR'+HCl}\begin{array}{l}\nearrow \mathrm{RH+R'HgCl}\\ \searrow \mathrm{R'H+RHgCl.}\end{array}$$

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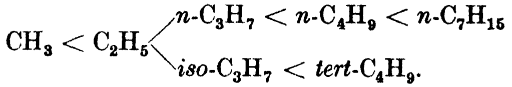
[30] Dippy and Lewis, *J.C.S.* 1936, 644.

[31] *J. Amer. Chem. Soc.* 1932, 54, 674.

If R is more electron-repulsive (electropositive) than R′, hydrogen will combine preferentially with the latter, giving the hydrocarbon R′H in larger quantity than RH, and the product will contain a higher proportion of RHgCl than of R′HgCl. Treatment of various dialkyls in this manner led Kharasch and Flenner to the following order of increasing electron-repulsive character:



$$CH_3 < C_2H_5 \begin{array}{l} \diagup n\text{-}C_3H_7 < n\text{-}C_4H_9 < n\text{-}C_7H_{15} \\ \diagdown \mathit{iso}\text{-}C_3H_7 < \mathit{tert}\text{-}C_4H_9. \end{array}$$

Experiments of the same type, in which lead tetra-alkyls were employed, have given similar results,[32] viz. $CH_3 < n\text{-}C_4H_9$ and $CH_3 < n\text{-}C_5H_{11}$. The order of inductive effects has also been found in the directive influences of the groups R in the nitration of quinol methyl alkyl ethers $CH_3O \cdot C_6H_4 \cdot OR$[33] and of phenylalkylsulphones $C_6H_5 \cdot SO_2 \cdot R$,[34] in the velocities of formation of bisulphite compounds and oximes by aliphatic ketones,[35] and in the chlorination of a series of phenolic ethers $X \cdot C_6H_4 \cdot OR$ (an actual decrease in the effect of the group is found here, when R reaches *n*-heptyl).[36]

In a large number of instances, however, the observed effects of alkyl groups do not follow the order of their inductive effects. Although the reasons for the divergence are in some cases not yet understood, the known examples appear to be divisible into four categories, and brief mention will be made of each.

(*a*) The peculiar order of effects may be due to a change in reaction mechanism and not to any abnormality on the part of the alkyl group itself. In cases of this kind irregularities are observed only when a primary group is compared with a secondary or a tertiary, or a secondary with a tertiary group. Examples are found in the work of Hughes and Ingold upon the hydrolysis of methyl, ethyl, *iso*propyl, and *tert*-butyl halides, which is described in Chapter X.

(*b*) When linked directly to a conjugated or aromatic system, the groups methyl, ethyl, *iso*propyl, and *tert*-butyl depart from the order of their inductive effects (Me < Et < *iso*Pr < *tert*-Bu) for another reason. Under these conditions methyl exhibits a capacity for electron-release superior to that of the other groups, the most familiar example being the predominating substitution at the 2-position

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[32] Jones, Evans, Gulwell, and Griffiths, *J.C.S.* 1935, 43.

[33] Robinson and Smith, *J.C.S.* 1926, 392; 1927, 2647.

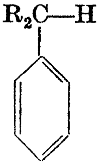
[34] Baldwin and Robinson, ibid. 1932, 1445.

[35] Stewart, ibid. 1905, 87, 185, 410.

[36] B. Jones, ibid. 1935, 1831.

(i.e. *ortho* to CH_3) in *p*-ethyl, *p*-*iso*propyl, and *p*-*tert*-butyl-toluenes.[37] Baker and Nathan[38] have postulated a mechanism of electron-release by alkyl groups which is distinct from and additional to that which arises from their inductive effects. They suggest that the electron pair (or pairs) linking carbon to hydrogen in one of the groups $—CH_3$, $—CH_2R$, or $—CHR_2$ may come under the influence of the adjacent carbon nucleus, giving rise, in a conjugate system, to an effect which is superimposed upon and is of the same sign as the inductive effect. This effect is of a permanent character, and may accelerate or retard a chemical change. It may be described as the 'mesomeric effect' of the alkyl group, for it depends upon resonance between structures such as I, II, and III, and it may be represented as in IV and V.

I



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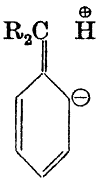

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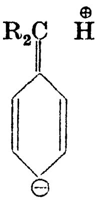

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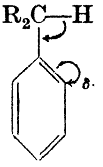
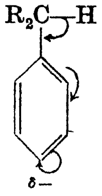


V



Since, in the groups CH_3, CH_3CH_2, $(CH_3)_2CH$, $(CH_3)_3C$, three, two, one, and no hydrogen atoms respectively may be concerned in a process of this kind, the effect decreases in magnitude in the order methyl > ethyl > *iso*propyl and becomes zero in *tert*-butyl (the reverse of the order of inductive effects). At the demand of a reagent the mesomeric effect may develop into an electromeric effect, and it is therefore most powerful when the reaction is strongly electron-demanding. Evidence for the existence of such an effect has come from studies of both velocity and equilibria, but in most cases it is not sufficiently important, relatively to the inductive effect, to place the groups in the order appropriate to itself; although, therefore, the order of groups is frequently disturbed, they show only small differences and a partially inverted sequence. Thus, the dissociation constants of the *p*-alkylbenzoic acids $R \cdot C_6H_4 \cdot COOH$ are as follows:[39]

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[37] Le Fèvre *et al.*, ibid. 1933, 980; 1934, 1501, 1696. Brady and Day, ibid., p. 114.

[38] Ibid. 1935, 1844. Compare Baker, ibid. 1939, 1150. A similar but not identical suggestion was made previously by Burkhardt and Evans (*Mem. Manchester Phil. Soc.* 1933, 77, 37).

R	CH_3	CH_3CH_2	$(CH_3)_2CH$	$(CH_3)_3C$
10^5K	4·24	4·43	4·43	3·98

while the dipole moments of the alkylbenzenes show the order of inductive effects (the values for toluene, ethylbenzene, *iso*propylbenzene, and *tert*-butylbenzene are 0·37, 0·58, 0·65, and 0·70 D respectively).[40] In the reactions where disturbances of the order of the groups have been detected, also, the velocity differences are usually small and the order quite irregular. During their recent work on aliphatic substitution, however, Hughes, Ingold, and Taher[41] have measured the velocities of hydrolysis of the *p*-alkylbenzhydryl chlorides in 80 per cent. acetone. The reaction is unimolecular, the measured stage being $RCl \rightarrow R^+ + Cl^-$, and is so strongly electron-demanding that the tautomeric (= mesomeric+electromeric) effect of the alkyl group is greatly magnified and the velocities stand in the order methyl > ethyl > *iso*propyl > *tert*-butyl (the actual figures for 10^6k at 0° are as follows: methyl, 83·5; ethyl, 62·6; *iso*propyl, 46·95; *tert*-butyl, 35·9).

(*c*) In 1930 Bennett and Mosses suggested that the methyl group exerts a field effect opposite in sign to its inductive effect.[42] Such an effect would have greatest influence at a point of the molecule which can approach the methyl group closely, and the rather high dissociation constant of *n*-butyric acid was cited as an example of its operation. A recent modification of this view postulates the formation of a hydrogen bond[43] between carbonyl oxygen or a similar electron-donating atom and a suitably placed carbon atom of an alkyl chain, a suggestion which is in reality an extension of the earlier views of Sidgwick and Callow.[44] The suggestion has been made by Evans[45] in order to interpret his observations of the prototropy of side-chain alkylated acetophenones. The energy of activation for the acid-catalysed prototropy of propiophenone, $CH_3 \cdot CH_2 \cdot CO \cdot C_6H_5$, is some 2,000 calories higher than that found for acetophenone, $H \cdot CH_2 \cdot CO \cdot C_6H_5$, and further lengthening of the chain has practically no effect. This marked increase in E, which is double that

[39] Baker, Dippy, and Page, *J.C.S.* 1937, 1774.

[40] Baker and Groves, ibid. 1939, 1144.

[41] Ibid. 1940, 949. See Summary in Chap. X.

[42] Ibid. 1930, 2364. Compare Ayling, ibid. 1938, 1014.

[43] See Chap. I, p. 22.

[44] See Chap. XV.

[45] *J.C.S.* 1936, 785. Evans and Gordon, ibid. 1938, 1434.

observed if a *p*-nitro-group is introduced into the nucleus, is accompanied by a rise of about a power of 10 in the value of the P factor of the kinetic equation, and Evans postulates the formation, in the transition complex, of a hydrogen bond between the carbonyl oxygen and the β-carbon atom of propiophenone and higher ketones. The resulting decrease of electron-availability at the carbonyl oxygen will operate against the attack of the acid catalyst, giving rise to the observed increase in the energy of activation. The results of an accurate redetermination of the dissociation constants of a number of the normal saturated aliphatic acids have led Dippy to postulate a hydrogen bond in the anions of *n*-butyric and the higher acids; the values for these acids are displaced upwards as compared with those for acetic and propionic acids.[46]

(*d*) An effect peculiar to ethyl is indicated by the unusually high basic strengths of dialkylanilines and dialkyltoluidines containing this group. They are illustrated by the following values for p_{KH} obtained by Hall and Sprinkle:[47]

Anilines

Dimethyl	5·06	Diethyl	6·56
Methyl ethyl	5·98	Dipropyl	5·59
Methyl propyl	5·64	Ethyl propyl	6·34

Toluidines

Ortho		*Para*	
Dimethyl	5·86	Dimethyl	5·50
Diethyl	7·18	Diethyl	7·09

A study of the directive influences of a number of alkoxyl groups in the nitration of guaiacol ethers *o*-$RO\cdot C_6H_4\cdot OCH_3$ by Allan and Robinson[48] showed a maximum at ethyl (the corresponding quinol ethers *p*-$RO\cdot C_6H_4\cdot OCH_3$ gave the theoretical order of inductive effects, as mentioned above). These peculiarities of the ethyl group find no obvious interpretation at present.

Before concluding this section, brief reference should be made to unsaturated groups.

Olefinic, and particularly acetylenic acids are stronger than the corresponding saturated acids, and this influence of the multiple linkage, like an inductive effect, is transmitted through a chain of saturated atoms and decreases in magnitude with increasing distance of the linkage from the carboxyl group. This is illustrated by the following dissociation constants for olefinic acids:[49]

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[46] Ibid. 1938, 1222.

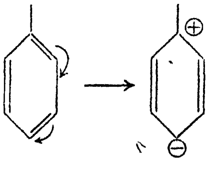
[47] *J. Amer. Chem. Soc.* 1932, **54**, 3469.

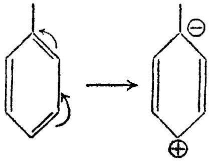
[48] *J.C.S.* 1926, 376. Compare ibid., p. 406.

Acid	10^5K_{therm}
$CH_3\cdot COOH$	1·76
$CH_2:CH\cdot COOH$	5·56
$CH_2:CH\cdot CH_2\cdot COOH$	4·62
$CH_2:CH\cdot CH_2\cdot CH_2\cdot COOH$	2·11
$CH_2:CH\cdot CH_2\cdot CH_2\cdot CH_2\cdot COOH$	1·90

Phenyl has a similar effect, 10^5K for phenylacetic and β-phenylpropionic acids being 4·88 and 2·19 respectively. As Ingold points out, 'radicals such as ethenyl and phenyl are to be regarded as intrinsi attractors of electrons. The acetylenyl radical attracts electrons more strongly still. The theory of these effects is at present obscure.'[50]

The influence of phenyl is not described completely in terms of a rather weak effect of an inductive character, however. This effect, for example, cannot be responsible for observations such as the following: (*a*) aryl groups in general are *op*-directive; (*b*) phenyl linked directly to carbonyl leads to a very great decrease in the stability of the cyanohydrin, whereas it has but little effect if one saturated carbon atom be interposed between the groups;[51] (*c*) certain enols are stabilized by phenyl much as they are by carbonyl or cyano;[52] (*d*) aryl groups have the very specialized property of conferring stability upon free radicals.[53] These and numerous other experimental facts can be understood, however, if it is realized that phenyl can become quinonoid by reason of electromeric displacements in either of two directions, as indicated below, and the sign of the tautomeric effect will depend upon the particular system in which the group finds itself.[54] It is perhaps simplest, therefore, to ascribe to phenyl the polar characters represented as —I, ±T.





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[49] Ives, Linstead, and Riley, *J.C.S.* 1933, 561; Dippy and Lewis, ibid. 1937, 1008.

[50] *Chem. Reviews*, 1934, 15, 239.

[51] Lapworth and Manske, *J.C.S.* 1930, 1976.

[52] See Chap. XII, p. 167.

[53] Chap. VII.

[54] See Ingold, *Ann. Reports*, 1928, 25, 121.

Halogens. The halogens form very stable anions, and exhibit, to a marked degree, the power of drawing electrons towards themselves. Thus the alkyl halides have dipole moments of the order of 1·6 to 2·2 Debye units, and the halogenoacetic acids are all very much stronger than acetic acid itself. The strengths of these acids fall from fluoro- to iodo-acetic, indicating a decrease in the inductive effects (—I) in the order F $>$ Cl $>$ Br $>$ I, and the proportions of *m*-derivative formed in the nitration of the benzyl halides (decreasing from $C_6H_5\cdot CH_2F$ to $C_6H_5\cdot CH_2Br$) point to the same order. The relevant figures are as follows:

X	F	Cl	Br	I	H
10^5K_{class} for $X\cdot CH_2\cdot COOH$ . . .	217	155	138	75	1·8
Per cent. *m*-derivative in nitration of $C_6H_5\cdot CH_2X$[55]	17·5	12	7	. .	4

The properties of compounds having halogen linked to a saturated carbon atom thus show that the inductive effects of the halogens (—I) are of considerable magnitude, and fall from fluorine to iodine. The same electron-attractive character is evident when halogen is attached to the benzene nucleus; as a class, halogenated aromatic acids and phenols are stronger than the unsubstituted compounds, while bases are weaker; with rare exceptions (see below) the general order $NO_2 > Hal > H$ is maintained. The same applies to a large number of side-chain reactions, both of Type A and of Type B. The *main* influence is still the inductive effect of the halogen. It has already been pointed out, however, that this is now not the *only* effect which operates, a conclusion which is based on the following evidence:

(*a*) The dipole moments of the halogenobenzenes in the gas phase are as follows: C_6H_5F 1·57, C_6H_5Cl 1·73, C_6H_5Br 1·71. These are appreciably smaller than those of the corresponding alphyl halides, viz. CH_3F 1·81, CH_3Cl 1·87, CH_3Br 1·80, particularly in the case of fluorobenzene; the halogenobenzenes therefore have mesomeric moments.

(*b*) The halogens are *op*-directive. The unusual phenomenon of *op*-substitution accompanied by nuclear *deactivation* is here encountered. The relative rates of nitration of the halogenobenzenes (referred to the rate for benzene as unity) are C_6H_5F 0·15, C_6H_5Cl 0·033, C_6H_5Br 0·030, C_6H_5I 0·18.[56]

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[55] Flürscheim and Holmes, *J.C.S.* 1928, 1611; Ingold and Ingold, ibid., p. 2253.

(c) The strengths of the halogenated aromatic acids, phenols, and bases are not in the order which would be predicted on the basis of inductive effects.

(*d*) The same applies to the relative velocities of numerous side-chain reactions of nuclear halogenated compounds.

The table which follows gives the data relating to a number of compounds in which halogen is linked to the aromatic nucleus. The numbers refer to the following:

I. Dissociation constants (10^5K) of benzoic acids, $X \cdot C_6H_4 \cdot COOH$, in water at 25°.[57]

II. 10^5K for phenylacetic acids, $X \cdot C_6H_4 \cdot CH_2 \cdot COOH$, in water at 25°.[57]

III. $10^{11}K$ for phenols, $X \cdot C_6H_4 \cdot OH$, in 30 per cent. aqueous alcohol at 25°.[58]

IV. $10^{10}K$ for phenylboric acids, $X \cdot C_6H_4 \cdot B(OH)_2$, in 25 per cent. alcohol at 25°.[59]

V. 10^2k for alkaline hydrolysis of benzoic esters, $X \cdot C_6H_4 \cdot COOC_2H_5$, in 88 per cent. alcohol at 30°.[60]

VI. k for the reaction of benzyl chlorides, $X \cdot C_6H_4 \cdot CH_2Cl$, with potassium iodide in acetone at 20°.[61]

VII. $k_1 + k_2$ for the prototropy of $\alpha\gamma$-diphenylmethyleneazomethines in alcohol at 82° catalysed by sodium ethoxide.[62]

VIII. 10^2k for the hydrolysis of benzyl chlorides in 50 per cent. aqueous acetone at 84·5°.[61]

IX. $10^{12}K$ for anilines, $X \cdot C_6H_4 \cdot NH_2$, in 30 per cent. alcohol at 25°.[58]

The data are all of relatively recent date, and their accuracy may be relied upon. In cases I to VII the inductive effects of the halogens would lead to values *falling* in the order F > Cl > Br > I, while in cases VIII and IX they would be expected to *rise* in this order.

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[56] Bird and Ingold, *J.C.S.* 1938, 918.
[57] Dippy *et al.*, ibid. 1934, 161, 1888; 1935, 343; 1936, 644.
[58] Bennett, Brooks, and Glasstone, ibid. 1935, 1821.
[59] Bettmann, Branch, and Yabroff, *J. Amer. Chem. Soc.* 1934, **56**, 1865.
[60] Kindler, ref. **22**; *Annalen*, 1928, **464**, 278.
[61] Bennett and B. Jones, *J.C.S.* 1935, 1815.
[62] Shoppee, ibid. 1931, 1225; 1932, 696.

X =	*m*-NO_2	*m*-F	*m*-Cl	*m*-Br	*m*-I	*p*-F	*p*-Cl	*p*-Br	*p*-I	H
I	32·1	13·65	14·8	15·4	14·1	7 22	10·5	10·7	. .	6·27
II	10·8	. .	7·24	. .	6·93	5·68	6·45	6·49	6·64	4·88
III	. .	15·1	49·0	43·7	38·9	2·6	13·2	15·5	21·9	3·2
IV	69·0	11·0	13·5	14·6	. .	3·66	6·30	7·26	. .	1·97
V	311·0	. .	36·3	39·5	. .	9·39	21·2	24·2	24·9	4·9
VI	4·83	1·84	2·17	2·47	2·34	1·90	2·80	3·12	2·98	1·32
VII	147·0	. .	10·7	9·47	7·33	. .	7·83	7·09	6·82	. .
VIII	2·85	5·51	5·56	4·92	5·02	38·2	13·3	11·6	10·6	23·2
IX	. .	10·5	8·51	7·94	7·59	120·0	28·8	21·9	15·1	126·0

An inspection of these figures shows that halogen in the *m*-position is always electron-attractive, though to a lesser extent than the nitro-group; this is in harmony with the order of inductive effects, $NO_2 > Hal > H$. But the differences between the individual halogens are small, and this approximate equality in their effects points to the operation of a factor which is opposite in sign to the inductive effect, and which decreases from fluorine to iodine (i.e. in the same order as the inductive effects). The necessity for postulating an effect diminishing in this order was first pointed out by Baddeley and Bennett.[63] The strengths of the *m*-halogenophenols (III) present a striking example of its operation, for fluorine here appears to be markedly *less* electron-attractive than the other halogens in the *m*-position; throughout the nine series quoted above, indeed, the order of the *m*-halogen-substituted compounds is rarely that which would be expected on the basis of the inductive effects.

The operation of a second factor is still more evident when the halogen is in the *p*-position. The variations are now more marked and indicate usually an apparent *increase* in electron-attractive character from fluorine to iodine; a complete 'inversion' of the halogen order is the rule rather than the exception. Indeed, in cases III and VIII (above) fluorine in the *p*-position appears to be electron-repulsive relatively to *hydrogen*,[64] and *p*-F behaves throughout as though it were far less powerfully electron-attractive than the remaining halogens (for example, in case IX there is an approximate equality between F and H).

The data, viewed as a whole, make it imperative to postulate the operation of an effect which is electron-repulsive in nature, and which decreases in the order F > Cl > Br > I. Groves and Sugden[65] have recently found values for the mesomeric moments of the halogenobenzenes in this order, viz. C_6H_5F 1; C_6H_5Cl 0·97, C_6H_5Br 0·89, C_6H_5I 0·87 Debye units. This effect is doubtless a resonance phenomenon, and is therefore spoken of as the 'mesomeric effect' of the halogens. Its influence at the *m*-position may be ascribed to a feeble relay by an inductive mechanism. Thus far there is substantial agreement between different investigators, but no such agreement has been reached with regard to the genesis of the effect. It is usually assumed that halogen is comparable with other groups having unshared electrons, and that resonance occurs between structures such as I and II.[66]

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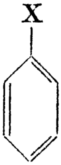
[63] *J.C.S.* 1933, 261.

[64] This peculiarity was first observed by Shoesmith and Slater, *J.C.S.* 1926, 217, in the hydrolysis of *p*-fluorobenzyl bromide.

[65] *J.C.S.* 1937, 1992.

I



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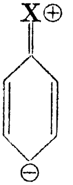
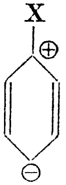


III



Bennett and his collaborators point out, however,[67] that of the four halogens fluorine must control its valence electrons the most powerfully and iodine, with the largest atom, least powerfully, and hence the magnitude of this effect should vary in the order

$$I > Br > Cl > F;$$

further, covalency increase between the substituent and nuclear carbon is here less probable than in the case of oxygen or nitrogen, since quinonoid forms of halogenated benzenes are not known. They therefore suggest that the dipolar unperturbed structures are of the type represented by III. Such a position might arise from the operation of a 'reversed field'. If the positive charge on the carbon atom of the C-Hal dipole is largely distributed throughout the nucleus, halogen will become virtually a negative pole and will thus develop electron-*repulsive* characters decreasing in the same order as the inductive effects. This will lead to the mesomeric state postulated.

It must be emphasized that, on either view, the magnitude of the mesomeric effect may vary with the system to which halogen is attached, and probably also with external conditions. The attacking reagent may also have some influence (e.g. electromeric effect[68]). The opposition to the inductive effect is thus not a constant quantity, and it is not surprising that the order of the halogens is different in different reactions, even in two reactions of the same series of compounds. The complications resemble those encountered in the case of alkyl groups, with the difference that the complete inversion of the order of inductive effects is the rule rather than the exception.

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[66] See, for example, Ingold, ref. 1; Robinson, ref. 1; Branch, ref. 59.

[67] Ref. 63, *J.C.S.* 1933, 1112; 1935, 1827.

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[68] See Oxford and Robinson, *J.C.S.* 1927, 2239; Robinson, ibid. 1933, 1114; Bird and Ingold, ref. 56.

VII

FREE RADICALS

THE term 'radical' was introduced into chemistry by Lavoisier. His ideas centred around oxygen, and he described inorganic compounds as the oxides of 'simple radicals' (elements) and organic compounds as the oxides of 'compound radicals' (containing at least the two elements carbon and hydrogen). He thus regarded sugar as the oxide of a hydrocarbon radical, and oxalic acid, got from sugar by oxidation, as a higher oxide of the same radical. The compound radical was, of course, purely hypothetical, but before very long examples were observed experimentally. In 1815 Gay-Lussac published the account of his investigation of the cyanogen compounds; he had prepared pure hydrocyanic acid and established its composition, and had further isolated cyanogen gas, which was believed to be the free radical. About seventeen years later, Liebig and Wöhler completed their study of the benzoyl radical. Starting from benzaldehyde they obtained a series of compounds in which the group C_7H_5O was present, and Laurent even claimed to have isolated the radical (his product was actually benzil). The third 'pillar' of the radical theory was the work of Bunsen (1839) upon the cacodyl compounds. He prepared a number of derivatives of the group $(CH_3)_2As$, and ultimately isolated cacodyl itself; this was not the radical, however, but had the doubled formula $[(CH_3)_2As]_2$. Aided by these and allied researches, the radical theory continued to dominate organic chemistry, which was actually described by Liebig in 1840 as 'the chemistry of the compound radical'.

The next stage was represented by the attempts of Frankland and Kolbe, between 1840 and 1850, to prepare the simple alphyl radicals. When, on heating ethyl iodide with zinc, Frankland obtained a gas of the empirical formula C_2H_5, he described it as the free ethyl radical, and Kolbe believed the product of the electrolysis of potassium acetate to be free methyl; the substances were actually the paraffins butane and ethane respectively. Although, however, Frankland and Kolbe did not succeed in their quest for the aliphatic radicals, they originated two important methods of synthesizing hydrocarbons; Frankland's method was modified by Wurtz (1854), who employed sodium in place of zinc, and the same process was applied by Fittig (1863) to the preparation of homologues of benzene. Thus there arose the synthetic methods which are familiar to every student of organic chemistry. Frankland's work, indeed, led also to the discovery of the metallic alkyls, and hence to the conception of valency.

Even after it was shown that the densities of the so-called 'radicals' were double those required by the formulae, a number of investigators still maintained that they were different from the 'isomeric' paraffins. It was Schorlemmer (1863) who proved the identity of these two sets of compounds. The terms free 'methyl' and 'ethyl' were then abandoned, and, with the development of the doctrine of valency and the success achieved by the structural theory with its assertion of the invariable quadrivalence of carbon, the conclusion was reached that the free radicals were incapable of existence. There the matter remained until the closing year of the last century.

Triarylmethyls and Allied Radicals.[1] The next phase in the history of the free radical opened with Gomberg's attempt, in 1900, to prepare hexaphenylethane by treatment of triphenylmethyl chloride with metallic silver.[2] The anticipated reaction was

$$2(C_6H_5)_3CCl+2Ag = 2AgCl+(C_6H_5)_3C\cdot C(C_6H_5)_3.$$

In the absence of atmospheric oxygen he obtained a colourless, crystalline solid having the analysis of the desired hydrocarbon. Its properties were quite unexpected, however. It gave yellow solutions in organic solvents, and, far from being a relatively inert substance, exhibited intense chemical reactivity, forming addition products with many elements and compounds. Thus, it gave a peroxide with oxygen, triphenylmethyl halides with halogens, triphenylmethane with hydrogen in presence of platinum, and solid crystalline products with a variety of organic compounds.[3] A determination of its molecular weight in naphthalene[4] gave a value of 415, whereas the molecular weight of hexaphenylethane is 486, and the observations were explained by postulating partial dissociation of the hydrocarbon into triphenylmethyl radicals having 'trivalent' carbon,

$$(C_6H_5)_3C\cdot C(C_6H_5)_3 \rightleftarrows (C_6H_5)_3C— + —C(C_6H_5)_3,$$

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[1] For excellent reviews of this subject see Gomberg, *Chem. Reviews*, 1924, **1**, 91: Ingold, *Ann. Reports*, 1924, **21**, 115; 1928, **25**, 150.

[2] *Ber.* 1900, **33**, 3150.

[3] Various papers by Gomberg, Schmidlin, Schlenk, and their collaborators.

[4] Gomberg, *Ber.* 1904, **37**, 2049.

the radical being present to the extent of 10 per cent. under the conditions employed in the cryoscopic measurement. The observed molecular weights in various solvents indicated proportions of the radical varying from 5 to 17 per cent. Further cryoscopic measurements by Schlenk and his collaborators[5] gave results which pointed to still larger percentages of other triarylmethyls in solutions of the corresponding hydrocarbons, e.g.

$$\begin{array}{ccc} (C_6H_5\cdot C_6H_4)C(C_6H_5)_2, & (C_6H_5\cdot C_6H_4)_2C\cdot C_6H_5, & (C_6H_5\cdot C_6H_4)_3C. \\ \text{15 per cent.} & \text{80 per cent.} & \text{100 per cent.} \end{array}$$

The demonstration of an equilibrium in these solutions was given by Schmidlin.[6] He found that a freshly made solution of hexaphenylethane was colourless for a few seconds, when a yellow colour developed and reached a permanent intensity; air removed the colour (formation of peroxide), which then reappeared. These changes could be repeated a number of times.

The solutions containing triarylmethyls were of more than one kind.[7] When hexaphenylethane was dissolved in a non-ionizing medium such as benzene, a non-conducting solution resulted, but in liquid sulphur dioxide it was conducting. In the latter case, therefore, the presence of positive and negative ions must be inferred,

$$(C_6H_5)_3C\cdot C(C_6H_5)_3 \rightleftarrows (C_6H_5)_3C^{\oplus}+C(C_6H_5)_3^{\ominus}.$$

These solutions have different absorption spectra. There are, therefore, three triphenylmethyls, the neutral radical and the two ions. This view is confirmed by the observation that solutions of triphenylmethyl chloride in liquid sulphur dioxide or hydrocyanic acid conduct the current, i.e.

$$(C_6H_5)_3CCl \rightleftarrows (C_6H_5)_3C^{\oplus}+Cl^{\ominus},$$

and that sodium and potassium form solid red compounds $NaC(C_6H_5)_3$ and $KC(C_6H_5)_3$, which also give conducting solutions (e.g. in liquid ammonia),[8] i.e.

$$NaC(C_6H_5) \rightleftarrows Na^{\oplus}+C(C_6H_5)_3^{\ominus}.$$

The colours of these different solutions indicate that the neutral triphenylmethyl radical and the kation are yellow, while the anion is red. A red benzyl anion is found in solutions of sodium benzyl in ether;[9] alkyl and aryl ions are, indeed, not uncommon, and their participation in many reactions has been demonstrated.[10] In the formation of an ion a covalent bond is broken unsymmetrically, both electrons remaining with one fragment, whereas the production of a neutral free radical involves the symmetrical rupture of the bond, one electron remaining with each portion of the molecule. The properties and stabilities of the radical and the ion may obviously differ as considerably as do, for example, those of halogen atoms and halide ions. It is the neutral radicals which form the subject of this chapter.

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[5] *Annalen*, 1910, **372**, 1; 1912, **394**, 180.

[6] *Ber.* 1908, **41**, 2471.

[7] Gomberg and Sullivan, *J. Amer. Chem. Soc.* 1922, **44**, 1810.

[8] Schlenk and Marcus, *Ber.* 1914, **47**, 1664; Kraus and Kawamura, *J. Amer. Chem. Soc.* 1923, **45**, 2756; Kraus and Rosen, ibid. 1925, **47**, 2739.

Reference has already been made to the paramagnetism of free radicals, and its use in their detection.[11] They are 'odd molecules', that is, they contain an odd number of electrons, whereas the compounds having the double formulae, of course, are not; the radical is paramagnetic and the compound is not, therefore. Paramagnetism has been observed experimentally in the triarylmethyls $C_{10}H_7 \cdot C(C_6H_5)_2$ and $(p\text{-}NO_2 \cdot C_6H_4)_3C$,[12, 13] and analogous examples are mentioned below.

The highly coloured (blue or green) and reactive metal ketyls formed by the interaction of an alkali metal with a diaryl ketone or aryl aldehyde,[14]

$$R_2C{=}O + Na = R_2C{-}ONa,$$

have properties resembling those of the radicals dealt with above. The single formulae of the compounds from potassium and phenyl-*p*-diphenylyl ketone or benzophenone have been demonstrated by molecular weight determinations[15] and by their paramagnetism.[16] Ketyls of the aliphatic series have also been prepared;[17] examples are those from di-*tert*-butyl and *iso*propyl-*tert*-butyl ketones. Certain acetophenones with branched side-chains also give rise to stable ketyls;[18] branched aliphatic chains thus favour the formation of such compounds, and similar observations have been made with regard to the dissociation of dialphyl-tetra-arylethanes.[19]

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[9] Schlenk and Holtz, *Ber.* 1917, **50**, 262.

[10] See Chap. X.

[11] p. 63.

[12] Taylor, *J. Amer. Chem. Soc.* 1926, **48**, 858.

[13] Allen and Sugden, *J.C.S.* 1936, 440.

[14] Schlenk and Weichel, *Ber.* 1911, **44**, 1182.

[15] Schlenk and Thal, *Ber.* 1913, **46**, 2840.

[16] Sugden, *Trans. Faraday Soc.* 1934, **30**, 18.

[17] Favorski and Nazarov, *Compt. rend.* 1933, **196**, 1229.

[18] Idem, *Compt. rend. Acad. Sci. U.R.S.S.* 1934, **1**, 325.

[19] Conant and Schultz, *J. Amer. Chem. Soc.* 1933, **55**, 2098.

Brief reference must be made to examples of 'abnormal valency' exhibited by nitrogen and oxygen. The dissociation of the tetraarylhydrazines, e.g.

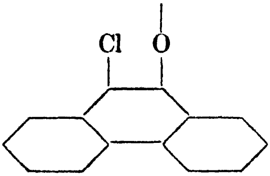
$$(C_6H_5)_2N{-}N(C_6H_5)_2 \rightleftarrows 2(C_6H_5)_2N{-},$$

was first demonstrated by Wieland,[20] who observed that solutions of tetraphenylhydrazine in boiling toluene were green in colour, and gave an addition product with nitric oxide. Hexa-aryltetrazanes also give deep blue solutions and combine with nitric oxide, indicating dissociation to hydrazyls,

$$Ar_2N{-}NAr{-}NAr{-}NAr_2 \rightleftarrows 2Ar_2N{-}NAr{-}.$$

(Ar = an aryl group)

These radicals have been investigated by Goldschmidt and his collaborators.[21] Diphenyl-picryl-hydrazyl is a remarkably stable radical, forming crystals resembling permanganate; it is reduced instantaneously by hydroquinone, a reaction which enabled Goldschmidt to demonstrate the existence of an equilibrium, by a procedure similar to that used by Schmidlin in the case of triphenylmethyl. The paramagnetism of diphenyl-trinitrophenyl-hydrazyl indicates at least 90 per cent. of the free radical in the solid state.[13] Goldschmidt found further[22] that oxidation of guaiacol by lead peroxide gave a green solution, suggesting the presence of $CH_3O \cdot C_6H_4 \cdot O{-}$; in a phenanthrene derivative the blue radical



and the corresponding compound of doubled formula (colourless) were both isolated, and 69 per cent. dissociation found in solution. Recent work by Schönberg[23] points to the formation of radicals in solutions of diaryl sulphides, $ArS \cdot SAr \rightleftarrows 2ArS{-}$.

All stable free radicals are characterized by the presence of aryl groups, and these groups make possible a large number of unperturbed structures, thus conferring upon the radical a considerable resonance energy. It is to this resonance energy that the stability of the radical is due.[24] Groups such as diphenylyl and naphthyl contribute more to the stability of the molecule than phenyl does, on account of the larger number of unperturbed structures which they make possible.

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[20] Wieland *et al.*, *Annalen*, 1911, **381**, 200; *Ber.* 1912, **45**, 2600; 1915, **48**, 1078.

[21] *Ber.* 1922, **55**, 616; *Annalen*, 1924, **437**, 194.

[22] *Ber.* 1922, **55**, 3194; *Annalen*, 1924, **438**, 202.

[23] *Ber.* 1932, **65**, 1864; 1933, **66**, 237, 1932; *Trans. Faraday Soc.* 1934, **30**, 17.

Aliphatic Free Radicals. The majority of organic compounds, when heated at temperatures between 500° and 1,000°, decompose into simpler substances,[25] and during the past forty years it has frequently been suggested that the primary change in many of these decompositions is the production of free radicals. Thus Nef,[26] as early as 1897, interpreted a number of thermal decompositions in the light of a free radical mechanism, and Bone and Coward, in 1908,[27] postulated 'residues' such as $>\mathrm{CH}$, $>\mathrm{CH_2}$, and $-\mathrm{CH_3}$ as intermediates in the pyrolysis of hydrocarbons. Later, Hinshelwood[28] demonstrated the homogeneous and unimolecular character of the thermal decompositions of a number of simple organic compounds including acetone and various ethers, and he represented the *initial stage* in each case as a cleavage of the molecule into radicals.

Alkyl ions have long been recognized in positive ray tubes,[29] but the proof of the existence of free aliphatic radicals did not emerge until 1929, when Paneth and Hofeditz[30] showed that lead tetramethyl can be decomposed by heat into metallic lead and free methyl groups. The vapour of the metallic alkyl, largely diluted with pure hydrogen and under a pressure of about 2 mm., was passed through a quartz tube at 500°–600°. A deposit of lead was formed, and the gaseous product removed a lead mirror placed near the outlet to the tube, with production of a compound which again could be decomposed by heat to give metallic lead. Other metals were attacked similarly (tellurium appears to be particularly useful for this purpose), and when zinc was employed the product was identified as zinc dimethyl. Neither hydrogen nor any of the hydrocarbons which were possible products of the decomposition reacted with metallic mirrors in this way, and almost identical results were obtained with nitrogen or helium as transport gas.[31] The demonstration of the real though transitory existence of the methyl radical was complete; its half-life was shown to be of the order 10^{-3} sec. Soon after, the ethyl radical was detected by a similar method;[32] above 600° it decomposes to give methyl.[33] Attempts to observe the higher alphyl radicals were unsuccessful, however, and it appears that they are too unstable for detection under these conditions; benzyl was identified, however, in the products of thermal decomposition of tin tetrabenzyl.[34] Paneth and Loleit[33, 35] have used the methyl and ethyl radicals in the synthesis of a number of arsenic, antimony, and bismuth alkyls, including the antimony analogue of cacodyl, $[Sb(CH_3)_2]_2$, which was thus prepared for the first time.

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[24] Pauling and Wheland, *J. Chem. Physics*, 1933, **1**, 362. Hückel, *Z. Physik*, 1933, **83**, 632; *Trans. Faraday Soc.* 1934, **30**, 40. Ingold, ibid. p. 52. The relative stabilities of radicals containing substituted aryl groups have also been studied (e.g. recent papers by Bowden, *J.C.S.* 1939 and 1940).

[25] See Hurd, *Pyrolysis of Organic Compounds* (Chemical Catalog Co., New York, 1929).

[26] *Annalen*, 1897, **298**, 202.

[27] *J.C.S.* 1908, **93**, 1197. Compare Bone, *Trans. Faraday Soc.* 1934, **30**, 148.

[28] See *Kinetics of Chemical Change* (Oxford University Press, 1940).

[29] Sir J. J. Thomson, *Rays of Positive Electricity* (Longmans, 1913).

[30] *Ber.* 1929, **62**, 1335.

Organo-metallic compounds are not the only sources of free aliphatic radicals. F. O. Rice and his collaborators[36] have shown that radicals are formed in the decompositions of organic compounds of various types, including hydrocarbons, aldehydes, ketones, and ethers. The radicals were identified by allowing them to combine with mercury; the mercury dialkyls thus formed react quantitatively with mercuric halides according to the equation

$$HgR_2+HgX_2 = 2RHgX, \qquad \text{e.g. } Hg(CH_3)_2+HgI_2 = 2(CH_3)HgI,$$

and the alkyl mercuric halides can be isolated as crystalline compounds with definite melting-points. The thermal decompositions were carried out at temperatures between 800° and 1,000°, and the work was simplified on the experimental side by the use of a condensable transport gas such as carbon dioxide or steam. In general, the results of Paneth were confirmed; methyl and ethyl were found to have half-life periods of about 10^{-3} sec., and no higher radicals were observed; methane, ethane, propane, and butane yielded no appreciable quantities of any radical other than methyl, and the same applies to acetone and diethyl ether.[37]

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[31] Paneth and Herzfeld, *Z. Elektrochem.* 1931, **37**, 577.
[32] Paneth and Lautsch, *Ber.* 1931, **64**, 2702.
[33] Paneth and Loleit, *J.C.S.* 1935, 366.
[34] Paneth and Lautsch, ibid., p. 380.
[35] *Trans. Faraday Soc.* 1934, **30**, 179.
[36] Rice, Johnston, and Evering, *J. Amer. Chem. Soc.* 1932, **54**, 3529.
[37] Rice and Evering, ibid. 1934, **56**, 2105; Rice and Dooley, ibid., p. 2747.

Both Paneth and Rice were thus unable to detect alphyl radicals higher than ethyl in the products of decomposition of organic compounds at 500° to 1,000°. During an investigation of a number of alkyl gold cyanides, however, Burawoy and Gibson found that the decomposition of derivatives such as di-*n*-propylmonocyanogold and di-*n*-propyldicyanodigold at temperatures not exceeding 120° gave substantially pure hexane, which was most probably the result of the combination of two *n*-propyl radicals.[38] The previous workers had obtained lower hydrocarbons in cases where these radicals were to be expected, but it would appear that at the temperature of decomposition of the alkyl gold cyanides the *n*-propyl radical exists for a sufficient period of time to permit combination to give hexane.

The formation of radicals in a reaction of quite a different type has been demonstrated by Polanyi and his collaborators.[39] Sodium vapour, diluted with hydrogen, methane, or nitrogen, was mixed with a gaseous methyl or ethyl halide, and the product allowed to react with chlorine or iodine. The formation of methyl and ethyl radicals was thus demonstrated, e.g. $Na+C_2H_5Br = NaBr+C_2H_5$; they were recognized at distances up to 8 cm. from the source.

Free Radicals in Photochemical Decompositions. Investigations of the photochemical decompositions of ketones have led Norrish and his collaborators to the conclusion that the primary change consists frequently of a cleavage into radicals.[40] Carbonyl compounds (in the gas phase) undergo two main types of photochemical decomposition, which may occur concurrently. The first type leads to the elimination of carbon monoxide and the production of one or more hydrocarbons. Aldehydes give very high yields of a single hydrocarbon,

$$R\cdot CHO \longrightarrow RH+CO,$$

whereas ketones give a mixture of hydrocarbons, the sum total being equivalent to the carbon monoxide:

$$R\cdot CO\cdot R' \longrightarrow (R_2+RR'+R_2')+CO,$$

e.g. $$CH_3\cdot CO\cdot C_2H_5 \longrightarrow (C_2H_6+C_3H_8+C_4H_{10})+CO.$$

As the chain of the aldehyde or ketone increases in length, decomposition of the second type becomes more prominent; the chain is ruptured at the $\alpha\beta$ position, to form olefin and a lower aldehyde or ketone; e.g.

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[38] *J.C.S.* 1935, 1024.

[39] Hartel and Polanyi, *Z. physikal. Chem.* 1930, **11**, 97; Hartel, *Trans. Faraday Soc.* 1934, **30**, 187; Horn, Polanyi, and Style, ibid., p. 189; *Z. physikal. Chem.* 1933, **23**, 291.

[40] See *Trans. Faraday Soc.* 1934, **30**, 103; *J.C.S.* 1934, 874, 1456; 1935, 1504; 1938, 1521, 1531.

$$CH_3{\cdot}CH_2{\cdot}CH_2\ {\cdot}CH_2{\cdot}CO{\cdot}CH_3 \longrightarrow CH_3{\cdot}CH{:}CH_2+CH_3{\cdot}CO{\cdot}CH_3,$$

In a third type of decomposition, which occurs far less frequently, a ketone gives rise to olefin and aldehyde; e.g.

$$CH_3{\cdot}CO{\cdot}C_2H_5 \longrightarrow CH_3{\cdot}CHO+C_2H_4.$$

A study of the photochemical decompositions of aldehydes and ketones in hydrocarbon solvents has led to results of great interest. Decompositions of the second type, and also of the first type in the case of aldehydes, proceed as in the gaseous phase; the products are the same, and the velocity is not influenced to any great extent. The solvent has a profound effect upon the first type decompositions of ketones, however. At room temperature there is hardly any change at all, and at temperatures of 70°–100°, where decomposition occurs, the products are different from those found when the vapour is decomposed; e.g. for methyl ethyl ketone in medicinal paraffin or *iso*octane solution the products were methane, ethane, and carbon monoxide, instead of ethane, propane, butane, and carbon monoxide as produced in the gas phase. There was also some acetaldehyde present, and the solvent developed unsaturation.

It is concluded that the first step in the photochemical decomposition of ketones (by the first type) is a fission of the molecule into radicals, which produce carbon monoxide and hydrocarbons as follows:

$$\begin{gathered} R{\cdot}CO{\cdot}R' \longrightarrow R{\cdot}CO+R', \\ R{\cdot}CO \longrightarrow R+CO, \\ 2R \longrightarrow R_2, \qquad R+R' \longrightarrow RR', \qquad 2R' \longrightarrow R'_2. \end{gathered}$$

When the decomposition occurs in a paraffin solvent, however, there is reaction between the solvent and the radicals, provided the temperature is sufficiently high. The radicals extract hydrogen from the solvent, thus becoming converted to hydrocarbon molecules, and the new radicals thereby derived from the solvent give rise to unsaturated hydrocarbons. The series of changes is of the following type:

$$\begin{array}{l} R{\cdot}CO{\cdot}R' \longrightarrow R{\cdot}CO+R' \\ \left\{\begin{array}{l} R{\cdot}CO+C_nH_{2n+2} \longrightarrow R{\cdot}CHO+C_nH_{2n+1} \\ R{\cdot}CO \longrightarrow R+CO \end{array}\right. \\ \left\{\begin{array}{l} R+C_nH_{2n+2} \longrightarrow RH+C_nH_{2n+1} \\ R'+C_nH_{2n+2} \longrightarrow R'H+C_nH_{2n+1} \end{array}\right. \\ 2C_nH_{2n+1} \longrightarrow C_nH_{2n}+C_nH_{2n+2}. \end{array}$$

The radicals formed initially are enclosed in a 'cage' of solvent molecules, and at ordinary temperatures will recombine; only when the temperature is as high as about 70° is the reaction of the paraffin with the radicals sufficiently rapid to render the above series of changes important.

The remaining photochemical decompositions referred to above appear to occur in one act without the intervention of radicals, although radicals must be involved to some extent in the decompositions of aldehydes, and the radical mechanism becomes more important as the frequency of the light and the temperature increase; further reference is made to this below.

The production of radicals in the photochemical decompositions of ketones has been confirmed by Pearson and his collaborators, who have been able to demonstrate, by the Paneth mirror method, the presence of radicals in the products of the action of ultra-violet light upon acetone and methyl ethyl, methyl *n*-propyl, methyl *iso*propyl, methyl *n*-butyl, diethyl, di-*n*-propyl, di-*iso*propyl, di-*sec*-butyl, and di-*tert*-butyl ketones.[41] Radicals were also found in the decomposition of acetaldehyde, though in relatively small quantity. In the case of di-*n*-propyl ketone, the vapours were passed over mercury and the product allowed to react with mercuric bromide. *n*-Propylmercury bromide was formed, the isolation of the *n*-propyl radical thus being demonstrated.[42]

The recent work of Pearson and his collaborators has also led to the definite detection of the methylene and phenyl radicals.[43] The production of methylene as an intermediate was postulated by Nef[26] and by Bone and Coward,[27] but the first direct evidence of its existence was obtained by Norrish and co-workers in a study of the photochemical decomposition of keten and of diazomethane.[44] Rice and Glasebrook's claim to have obtained methylene was later doubted by the authors themselves,[45] and Paneth and Lautsch failed to observe the radical in many reactions where its liberation was probable.[34] Pearson, Purcell, and Saigh have now described the isolation of methylene from both keten and diazomethane, and by both thermal and photochemical decomposition; it was caused to form telluroformaldehyde CH_2Te by reaction with a tellurium mirror, and this compound was identified; selenium mirrors similarly gave selenoformaldehyde CH_2Se. The production of diphenyl by the thermal decomposition of lead tetraphenyl was regarded by Zartman and Adkins[46] and by Dull and Simons[47] as evidence of the presence of the phenyl radical, and Horn and Polanyi[48] claimed to have detected this radical in the reaction of sodium with bromobenzene vapour, but Paneth and Lautsch could find no evidence for its existence.[34] Glazebrook and Pearson have now found the phenyl radical (identified by the formation of phenylmethyl telluride) in the products of photochemical decomposition of acetophenone and of benzophenone.

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[41] *J.C.S.* 1934, 1718; 1935, 1151; 1936, 1777; 1937, 567.

[42] Ibid. 1936, 253.

[43] Ibid. 1938, 409; 1939, 589. *Trans. Faraday Soc.* 1939, **35**, 880.

[44] *J.C.S.* 1933, 119, 1533.

[45] *J. Amer. Chem. Soc.* 1934, **56**, 2381; *Chem. Reviews*, 1935, **17**, 60. See also Belchetz, *Trans. Faraday Soc.* 1934, **30**, 170.

Reactions in Solution involving Free Radicals. Ions are frequently formed in the intermediate steps of reactions in solution, whereas in the gaseous phase molecules dissociate almost universally into atoms or neutral radicals. Hey and Waters have now shown that certain reactions in solution, under suitable conditions, proceed by way of radicals.[49] The clearest instances are found in reactions of diazonium salts, diazotates, nitrosoacylanilides, and arylazotriarylmethanes. All these involve the elimination of a nitrogen molecule, which is comparable with the elimination of carbon monoxide from a carbonyl compound (as in the photochemical decompositions of ketones considered above).

The decomposition of benzenediazonium chloride in alcoholic solution may give rise to benzene or to an alkyl phenyl ether, and the proportions of the products vary with the alcohol used and the experimental conditions.[50] With methyl alcohol, for example, the predominating reaction is the formation of anisole in accordance with the equation

$$C_6H_5 \cdot N_2Cl + CH_3OH = C_6H_5 \cdot O \cdot CH_3 + N_2 + HCl,$$

whereas ethyl alcohol yields mainly benzene,

$$C_6H_5 \cdot N_2Cl + CH_3 \cdot CH_2OH = C_6H_6 + CH_3 \cdot CHO + N_2 + HCl.$$

In spite of the differences in the nature of the product, however, the rates of decomposition are almost the same for a series of alcohols,[51] and this is easily understood if the measured velocity is that of the formation of phenyl radicals from the diazonium salt. Such a view is confirmed by the observation that when benzenediazonium chloride decomposes under acetone in the presence of antimony, bismuth lead, mercury, and other metals, the metal is attacked even if the mixture is kept neutral with calcium carbonate.[52]

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[46] *J. Amer. Chem. Soc.* 1932, **54**, 3398.

[47] Ibid. 1933, **55**, 3898.

[48] *Z. physikal. Chem.* 1934, **25**, 151.

[49] *Chem. Reviews*, 1937, **21**, 169.

[50] Hantzsch and Jochem, *Ber.* 1901, **34**, 3337.

[51] Pray, *J. Physical Chem.* 1926, **30**, 1477.

The reactions between diazotates (from diazonium salts and excess alkali) and aromatic compounds have been utilized in the preparation of diphenyl derivatives:[53]

$$C_6H_5\cdot N_2\cdot ONa + C_6H_5R = C_6H_5\cdot C_6H_4R + N_2 + NaOH.$$

The reaction is peculiar in that the phenyl which enters the C_6H_5R as a substituent always takes up the *ortho*- or the *para*-position with respect to R, whether R be an *op*- or a *m*-directive group. The same phenomenon of invariable *op* substitution is met with when aromatic compounds react with nitrosoacetanilide (which is closely related to the diazotates, being tautomeric with benzene diazoacetate, $C_6H_5\cdot N(NO)\cdot COCH_3 \rightleftarrows C_6H_5\cdot N:N\cdot O\cdot COCH_3$); the reaction is

$$C_6H_5\cdot N(NO)\cdot COCH_3 + C_6H_5R = C_6H_5\cdot C_6H_4R + N_2 + CH_3\cdot COOH,$$

and the phenyl enters *para*- to R whatever be the nature of the latter. Further, the speed of evolution of nitrogen is the same for a series of aromatic compounds.[54] All these facts are in harmony with a mechanism which postulates the liberation of the phenyl radical as the first and measurable step, e.g.

$$C_6H_5\cdot N(NO)\cdot COCH_3 \longrightarrow C_6H_5 + N_2 + CH_3\cdot COO$$
$$C_6H_5 + C_6H_5R \longrightarrow C_6H_5\cdot C_6H_4R + H$$
$$CH_3\cdot COO + H \longrightarrow CH_3\cdot COOH.$$

Moreover, in solvents such as *n*-hexane, cyclohexane, and several others, benzene is formed, and methyl or ethyl iodide gives iodobenzene, which again points to the intervention of radicals,[55]

$$C_6H_5 + RH \longrightarrow C_6H_6 + R$$
$$C_6H_5 + RCl \longrightarrow C_6H_5Cl + R.$$

Phenylazotriphenylmethane, $C_6H_5\cdot N_2\cdot C(C_6H_5)_3$, in a hydrocarbon solvent at about 80°, gives triphenylmethyl radicals which have been identified,[56] and some benzene is formed, presumably from phenyl radicals liberated in the decomposition

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[52] Waters, *J.C.S.* 1937, 2007.

[53] Gomberg *et al.*, *J. Amer. Chem. Soc.* 1924, **46**, 2339; 1926, **48**, 1372.

[54] Grieve and Hey, *J.C.S.* 1934, 1797.

[55] Waters, ibid. 1937, 113.

$$C_6H_5\cdot N_2\cdot C(C_6H_5)_3 \longrightarrow C_6H_5+N_2+C(C_6H_5)_3.$$

Hey carried out the decomposition in the aromatic solvents benzene and chlorobenzene, and isolated diphenyl and 4-chlorodiphenyl respectively.[57] The case is exactly similar to those described above. All these reactions appear, therefore, to involve the liberation of highly reactive neutral phenyl radicals which do not polymerize to give diphenyl, but which react rapidly with aliphatic and aromatic compounds, the phenyl group taking up invariably the *o*- or *p*-position to a group already present.

Free Radicals in Chain Reactions. A chemical reaction does not usually proceed by way of the complete dissociation of the reagent molecules. Thus, in a change $AB+CD = AC+BD$ the formation of the links between A and C and between B and D occurs simultaneously with the rupture of those between A and B and between C and D, and the energy required is much less than that which would be necessary for the complete dissociation of AB and CD.[58] In some instances, however, the initial step is actually the production of free atoms or radicals, a process needing a much higher energy of activation than does the more usual mechanism; the free atom or radical, however, by virtue of its unsaturation, may now initiate further changes which require but little energy, and so a reaction chain is set up.[59] Instead of a relatively easy process which leads to no further consequences, a far more difficult initial step occurs, but is magnified enormously by subsequent processes to which it gives rise. Reaction chains are particularly frequent among photochemical processes, where they lead to an abnormally high quantum efficiency (number of molecules decomposed by each quantum of energy). The photochemical decompositions of formaldehyde and acetaldehyde, for example, have quantum efficiencies of unity at 100°, but these rise to the order of a hundred at 300° to 400°; reaction chains intervene to an important extent at the higher temperatures. In the case of acetone, however, the quantum efficiency never rises appreciably above unity, and thus chains are not indicated.[60]

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[56] Wieland *et al.*, *Ber.* 1922, **55**, 1816; *Annalen*, 1934, **514**, 145.

[57] *J.C.S.* 1934, 1966.

[58] See Chap. V.

[59] This may be defined as a 'Material Chain' as opposed to an 'Energy Chain' which is propagated by energized molecules of the product. For an account of the characteristics of Chain Reactions see Hinshelwood, ref. 28.

F. O. Rice has suggested that the *thermal* decompositions of organic compounds, a number of which have been shown (by Hinshelwood and others) to be unimolecular, are chain reactions involving free radicals.[61] He points out that the radical formed in the primary breakdown of the molecule may *either* decompose *or* withdraw hydrogen from another molecule, giving in each case a new radical; thus a reaction chain could be propagated; e.g.

$$\begin{aligned} CH_3\cdot CH_2\cdot CH_2\cdot CH_3 &\longrightarrow CH_3 + CH_3\cdot CH_2\cdot CH_2, \\ CH_3\cdot CH_2\cdot CH_2 &\longrightarrow CH_3 + CH_2{:}CH_2, \\ CH_3 + CH_3\cdot CH_2\cdot CH_2\cdot CH_3 &\longrightarrow CH_4 + CH_3\cdot CH_2\cdot CH_2\cdot CH_2, \\ CH_3\cdot CH_2\cdot CH_2\cdot CH_2 &\longrightarrow CH_3\cdot CH_2 + CH_2{:}CH_2, \end{aligned}$$

and so on. These free radical mechanisms do not affect the Hinshelwood-Lindemann view of unimolecular reactions, which would still apply to the primary rupture of the molecule. Subsequent work has not justified so sweeping a generalization as that made by Rice, however.

The demonstration that free radicals are present in the system at some stage of a reaction is not proof that a chain mechanism is operating. An excellent test for reaction chains, however, consists in the addition of a very small quantity of nitric oxide. This is an 'odd molecule', and combines with the radicals, thus breaking the chains; the absence of inhibition by nitric oxide is evidence that a chain mechanism is not involved. Staveley and Hinshelwood have examined a number of thermal decompositions by this method.[62] They find no inhibition of the decompositions of acetaldehyde, chloral, certain ketones, or methyl alcohol, and it may safely be concluded that reaction chains are not involved in these instances. On the other hand, a small quantity of nitric oxide causes a strong inhibition of the thermal decompositions of propionic and butyric aldehydes, of several ethers, and of ethane. These must therefore be chain reactions, though in all probability they do not proceed exclusively by the chain mechanism. In general it may be stated that chains are involved in the decompositions of some, though by no means all, organic compounds. Chain mechanisms are important but not universal.

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[60] Leermakers, *J. Amer. Chem. Soc.* 1934, **56**, 1537, 1899. Akeroyd and Norrish, *J.C.S.* 1936, 890.

[61] *J. Amer. Chem. Soc.* 1931, **53**, 1959; 1934, **56**, 284; *Chem. Reviews*, 1932, **10**, 135; 1935, **17**, 53; *Trans. Faraday Soc.* 1934, **30**, 152. F. O. Rice and K. K. Rice, *The Aliphatic Free Radicals* (Baltimore, Johns Hopkins Press, 1935).

[62] *Proc. Roy Soc.* 1936, **154** A, 335; *J.C.S.* 1936, 812; 1937, 1568. *Trans. Faraday Soc.* 1939, **35**, 845. Another method of detecting reaction chains has been used by Patat and Sachsse, *Naturwiss.* 1935, **23**, 247.

VIII

COMPOUNDS OF DIVALENT CARBON AND ALLIED PROBLEMS

THE divalency of carbon in carbon monoxide, the carbylamines (isocyanides), and the fulminates, was postulated by Nef,[1] who wrote these compounds as follows:

$$\mathrm{O{=}C}, \qquad \mathrm{R{-}N{=}C}, \qquad \mathrm{RO{-}N{=}C}.$$

A formula with a quadruple link between carbon and nitrogen or oxygen is inadmissible on stereochemical grounds, and is, moreover, inconsistent with the modern covalency rule which limits the valence groups of nitrogen and oxygen to eight electrons. The strongest argument in favour of the Nef formula was the fact that the chemical behaviour of these substances indicates that the unsaturation is confined to the carbon atom, as exemplified by the addition reactions

$$\mathrm{O{=}C + Cl_2 \rightarrow O{=}CCl_2} \text{ and } \mathrm{R{-}N{=}C + O \rightarrow R{-}N{=}C{=}O}.$$

An alternative representation, in which carbon shares *six* electrons with oxygen or nitrogen, was first suggested by Langmuir,[2] and was accepted by Lewis,[3] Sugden,[4] and others. Its correctness has recently been demonstrated by Sidgwick and his collaborators.[5] The compounds are therefore formulated

$$\mathrm{O}\overset{\rightarrow}{=}\mathrm{C}, \qquad \mathrm{R{-}N}\overset{\rightarrow}{=}\mathrm{C}, \qquad \mathrm{RO{-}N}\overset{\rightarrow}{=}\mathrm{C},$$

or

$$\overset{\oplus}{\mathrm{O}}\equiv\overset{\ominus}{\mathrm{C}}, \qquad \mathrm{R{-}}\overset{\oplus}{\mathrm{N}}\equiv\overset{\ominus}{\mathrm{C}}, \qquad \mathrm{RO{-}}\overset{\oplus}{\mathrm{N}}\equiv\overset{\ominus}{\mathrm{C}}.$$

In addition to the four-electron bond postulated by the Nef formula, a co-ordinate linkage is formed, the oxygen or nitrogen acting as donor, and carbon as acceptor; the octet of the latter is thus completed. The oxygen in carbon monoxide thereby becomes 'oxonium' in character, and the nitrogen of the carbylamines or fulminates has a fully shared octet. The carbon, however, has one unshared pair of electrons by means of which it can co-ordinate as donor, while if the co-ordinate bond is ruptured it can also act as acceptor. The formula is thus in harmony with the chemical characters of the compounds, the carbon being the reactive centre.

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[1] *J. Amer. Chem. Soc.* 1904, **26**, 1549, and references there cited. The formulae RNC for carbylamines (as opposed to RCN for nitriles) and CNOH for fulminic acid (as contrasted with NCOH for cyanic and HNCO for isocyanic acid) follow from the products of hydrolysis, as is well known.

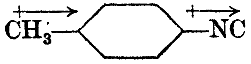
[2] *J. Amer. Chem. Soc.* 1919, **41**, 1543.

[3] *Valence and the Structure of Atoms and Molecules* (Chemical Catalog Co., New York, 1923), p. 127.

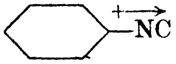
[4] *The Parachor and Valency* (Routledge & Sons, 1930), p. 171.

[5] Hammick, New, Sidgwick, and Sutton, *J.C.S.* 1930, 1876; Sidgwick, *Chem. Reviews*, 1931, **9**, 77; Sidgwick and Bowen, *Ann. Reports*, 1931, **28**, 396; Sidgwick, *The Covalent Link in Chemistry* (Cornell University Press, 1933), p. 187.

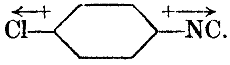
The evidence for these formulae was obtained by a study of parachors and dipole moments, and confirmation is found in the heats of formation, vibrational frequencies, and dimensions of the linkages. The values of the parachors for $N\overset{\rightarrow}{=}C$ and $N{=}C$ are calculated as 62·3 and 40·5 units respectively, and the mean value observed is 67 units, in fairly good agreement with the former.[6] For carbon monoxide the observed value of 61·6 is much nearer to that for $C\overset{\leftarrow}{=}O$ (69·6) than to that for $C{=}O$ (48·0).[7] There is some uncertainty here, however, as the effect of the carbon sextet in the Nef formula is unknown. The dipole moment evidence is more convincing. The moment of the $\rangle C{=}O$ bond in ketones and aldehydes has a relatively high value of between 2 and 3 Debye units; that found for carbon monoxide is indistinguishable from zero, indicating an opposing dipole such as would be anticipated on the basis of an additional co-ordinate bond. In the case of the aryl *iso*cyanides, the dipole of the —NC group has its negative end on carbon; this is shown by the fact that the observed moment of phenyl *iso*cyanide is increased by *p*-CH_3 and decreased by *p*-Cl:[8]



$\mu = 3{\cdot}98$

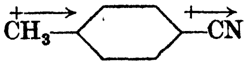


$\mu = 3{\cdot}49$

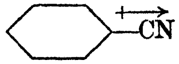


$\mu = 2{\cdot}07$

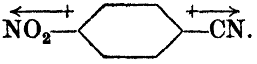
The moments of *p*-substituted benzonitriles, on the other hand, show that the nitrogen is here the negative end of the dipole, $\overset{\oplus}{C}\equiv\overset{\ominus}{N}$; the values are as follows:



$\mu = 4{\cdot}40$



$\mu = 3{\cdot}97$



$\mu = 0{\cdot}66$

This difference between the moments for the cyanide and *iso*cyanide groups can again be attributed to the presence of a co-ordinate bond in the latter. Much additional weight was given to the argument when New and Sutton[9] showed that the dipole moment of *p*-di*iso*cyanobenzene is indistinguishable from zero. The Nef formula, $C{=}N\cdot C_6H_4\cdot N{=}C$, would demand an angle of about 125° between the single and double bonds, and any orientation of the group would be possible between the extreme positions

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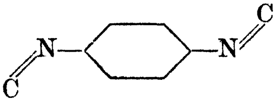
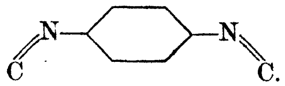
[6] Compare Lindemann and Wiegrebe, *Ber*. 1930, 63, 1650.

[7] Sugden, ref. 4.

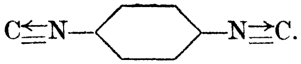
[8] See Chap. IV, p. 54.



and



A resultant moment as in *p*-phenylene diamine[10] would therefore be anticipated. On the other hand, the six-electron bond gives a linear structure which is therefore non-polar:



The zero moment of nickel carbonyl[11] leads to a similar conclusion for carbon monoxide, since the link between carbon and oxygen must be collinear with that joining the group to the metal.

Sidgwick points out, in confirmation, that the heats of formation of the links, their vibrational frequencies (about 2,000 $cm.^{-1}$ from Raman Spectra), and, in the case of carbon monoxide, the internuclear distance are all in harmony with those for a six-electron linkage. This structure also accounts for the similarity in physical properties between carbon monoxide and nitrogen gas, which was emphasized by Langmuir. Electron diffraction methods have now shown that the carbon-oxygen distances in carbon monoxide and nickel carbonyl and the carbon-nitrogen distances in cyanides and *iso*cyanides are all about the same.[12]

The tautomerism of acetylene, as postulated by Nef,

$$CH{\equiv}CH \rightleftharpoons CH_2{=}C,$$

cannot be interpreted in this way, since the octet of the first carbon is fully shared; such tautomerism does not appear to be indicated by physical properties.[13] The existence of divalent carbon compounds such as $C(OC_2H_5)_2$ is also very doubtful.[14]

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[9] *J.C.S.* 1932, 1415.

[10] Chap. IV, p. 58.

[11] Sutton, New, and Bentley, *J.C.S.* 1933, 652.

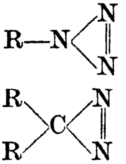
[12] Brockway, *J. Amer. Chem. Soc.* 1936, **58**, 2516; Brockway and Cross, *J. Chem. Physics*, 1935, **3**, 828.

[13] But see de Laszlo, *Trans. Faraday Soc.* 1934, **30**, 825.

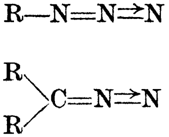
[14] Scheibler, *Ber.* 1926, **59**, 1022; Arbusov, ibid. 1931, **64**, 698.

Azides and Aliphatic Diazo-Compounds. The esters of hydrazoic acid, RN_3, and the derivatives of diazomethane, CR_2N_2, also present a structural problem of considerable difficulty. The possible formulae are of three types, viz.

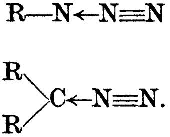
I



II



III



The original ring formulae (I) were later replaced by open-chain structures on account of the conversion of these substances into open-chain compounds by reduction and addition reactions. The chemical evidence is very inconclusive, however, while parachor values are of little use since those calculated for the alternative structures differ by small amounts only.

X-ray measurements on sodium and potassium azides and upon cyanuric azide show that both the N_3^- ion and the N_3 group are linear,[15] and a ring structure for the azides and aliphatic diazo-compounds is excluded also by the heat of formation of the azide group[16] and by the electron diffraction patterns of methyl azide and diazomethane vapours.[17] On the other hand, the dipole moments of aryl azides and of diaryldiazomethanes are much smaller than would be anticipated on the basis of either of the linear formulae,[16] and the boiling-points are similar to those of the corresponding halides, and much lower than those of analogous nitro-compounds.[18] Although, therefore, the ring formula I is excluded, neither of the highly polar representations II and III is in harmony with the facts.

Sidgwick has suggested that the compounds are resonance structures between the open-chain forms II and III; the predominant moments, those of the co-ordinate linkages, are equal and opposite, and resonance will lead to a resultant mesomeric structure of small moment.[16] This view is completely borne out by the interatomic distances found by the electron diffraction method,[17] and has met with general acceptance.

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[15] Hendricks and Pauling, *J. Amer. Chem. Soc.* 1925, **47**, 2904; Knaggs, *Proc. Roy. Soc.* 1935, **150** A, 576.

[16] Sidgwick, *Trans. Faraday Soc.* 1934, **30**, 801; Sidgwick, Sutton, and Thomas, *J.C.S.* 1933, 406.

[17] Brockway and Pauling, *Proc. Nat. Acad. Sci.* 1933, **19**, 860; Boersch, *Monatsh.* **1935**, **65**, 311.

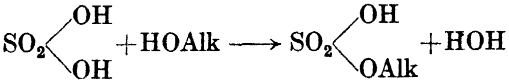
[18] Sidgwick, *J.C.S.* 1929, 1108.

IX

ESTERIFICATION AND HYDROLYSIS

ESTERIFICATION is an acid-catalysed reaction, the catalyst being either the esterifying acid itself (if sufficiently strong) or an added acid; catalysis by bases is obviously impossible. The velocity of esterification is proportional to the concentrations of alcohol, acid, and acid catalyst (and therefore, if the esterifying acid is itself the catalyst, to the square of its concentration). Typical esterifications are

$$\mathrm{HCl+HOAlk \longrightarrow AlkCl+HOH}$$



$$\mathrm{SO_2(OH)_2+HOAlk \longrightarrow SO_2(OH)(OAlk)+HOH}$$

$$\mathrm{R\cdot COOH+HOAlk \longrightarrow R\cdot COOAlk+HOH.}$$

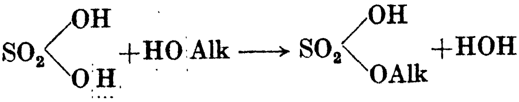
The reverse of esterification is acid-catalysed hydrolysis, e.g.

$$\mathrm{R\cdot COOAlk+HOH \longrightarrow R\cdot COOH+HOAlk,}$$

but esters may also be hydrolysed by alkali,

$$\mathrm{R\cdot COOAlk+OH' \longrightarrow R\cdot COO'+HOAlk.}$$

In esterification by halogen acids, and in the hydrolysis of their esters, it is obvious that the hydroxyl group of the alcohol molecule must be transferred intact to the water, and vice versa, since no other oxygen is available. Esterification by sulphuric acid or by a carboxylic acid can be formulated in two ways, however; the oxygen of the water might come from the alcohol, as in



$$\mathrm{SO_2(OH)(O\vdots H)+HO\vdots Alk \longrightarrow SO_2(OH)(OAlk)+HOH}$$

$$\mathrm{R\cdot COO\vdots H+HO\vdots Alk \longrightarrow R\cdot COOAlk+HOH}$$

or from the acid, as follows:

$$\mathrm{R\cdot CO\vdots OH+H\vdots OAlk \longrightarrow R\cdot COOAlk+HOH.}$$

Similarly, in hydrolysis the oxygen found ultimately in the alcohol might be derived either from the water or from the ester, i.e.

$$\mathrm{R\cdot COO\vdots Alk+HO\vdots H \longrightarrow R\cdot COOH+HOAlk,}$$

or $$\mathrm{R\cdot CO\vdots OAlk+H\vdots OH \longrightarrow R\cdot COOH+HOAlk.}$$

This problem was discussed by Ferns and Lapworth in 1912,[1] and they concluded that, whereas the group —SO$_2$OAlk of a sulphuric or sulphonic ester reacts with fission of the O—Alk bond, as in alkylation by an alkyl sulphate or the replacement of —MgX of a Grignard by an alkyl group, the O—Alk bond of the ester grouping —COOAlk remains intact. The point of division in the two cases, as envisaged by Ferns and Lapworth, was as follows:

$$\text{—SO}_2\text{—O—}\vdots\text{Alk} \quad \text{and} \quad \text{—CO}\vdots\text{—O—Alk.}$$

Reid[2] had already shown that the reaction of thiolbenzoic acid with ethyl alcohol and that of benzoic acid with ethyl mercaptan were to be represented

$$C_6H_5\cdot CO\vdots SH + H\vdots OC_2H_5 \longrightarrow C_6H_5\cdot COOC_2H_5 + HSH$$

$$C_6H_5\cdot CO\vdots OH + H\vdots SC_2H_5 \longrightarrow C_6H_5\cdot COSC_2H_5 + HOH.$$

It has now been demonstrated, by four different methods, that in the esterification of a carboxylic acid —OH from the acid unites with hydrogen from the alcohol to form water (oxygen from the alcohol passing into the ester), while in ester hydrolysis the —OAlk group from the ester is transferred intact to the alcohol. The processes are as follows, therefore:

$$R\cdot CO\vdots OH + H\vdots OAlk \longrightarrow R\cdot COOAlk + HOH$$

$$R\cdot CO\vdots OAlk + H\vdots OH \longrightarrow R\cdot COOH + HOAlk.$$

The methods by which these mechanisms have been proved are as follows:

1. If the ester R·COOAlk is optically active, the asymmetric carbon atom being that which links the group Alk to oxygen, the tetrahedral configuration of the valencies of this carbon atom will not be maintained if the group Alk becomes free at any stage of the hydrolysis.[3] The preservation of optical activity shows, therefore, that the O—Alk bond is not broken, and such preservation of asymmetry has been found in the alkaline hydrolysis of *l*-acetylmalic acid.[4] Similarly, an optically active alcohol in which the asymmetric carbon atom is linked to oxygen will give an optically active ester only if the O—Alk bond persists unbroken throughout the process, and Hughes, Ingold, and Masterman have observed a complete retention of optical activity in the esterification of *β*-*n*-octyl alcohol by acetic acid.[5]

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[1] *J.C.S.* 1912, **101**, 273.

[2] *Amer. Chem. J.* 1910, **43**, 489.

[3] See Wallis and Adams, *J. Amer. Chem. Soc.* 1933, **55**, 3838; also Shriner, Adams, and Marvel in Gilman's *Organic Chemistry*, New York, 1938, vol. 1, p. 303.

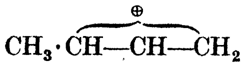
[4] Holmberg, *Ber.* 1912, **45**, 2997.

[5] *J.C.S.* 1939, 840.

2. If the alkyl group of the ester $\mathrm{R\cdot COOAlk}$ is such that it gives a mesomeric positive ion, the freedom of this ion at any stage of hydrolysis would give rise to a mixture of alcohols. Now crotyl acetate

$$\mathrm{CH_3\cdot CH{:}CH\cdot CH_2X} \quad (\mathrm{X} = \text{acetate})$$

and α-methylallyl acetate $\mathrm{CH_3\cdot CHX\cdot CH{:}CH_2}$ give the same mesomeric ion I, the unperturbed structures being II and III;

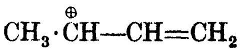


$\mathrm{CH_3\cdot}\overset{\oplus}{\overbrace{\mathrm{CH{-}CH{-}CH_2}}}$

I

$\mathrm{CH_3\cdot CH{=}CH{-}\overset{\oplus}{C}H_2}$

II



$\mathrm{CH_3\cdot \overset{\oplus}{C}H{-}CH{=}CH_2}$

III

If this ion ever became free, hydrolysis of either ester would give a mixture of crotyl and methylallyl alcohols, but in actual fact each ester gives its own alcohol whether the hydrolysis be acid or alkaline.[6]

3. In a recent investigation, *neo*pentyl alcohol $\mathrm{(CH_3)_3C\cdot CH_2OH}$ was esterified with acetic, chloroacetic, dichloroacetic and trichloroacetic acids, and the product hydrolysed with potassium hydroxide.[7] In each case *neo*pentyl alcohol was recovered unchanged, and no unsaturated compounds were formed. Now the work of Whitmore[8] has shown that a positive *neo*pentyl group invariably rearranges to *tert*-amyl, unsaturated derivatives being formed simultaneously, and the result therefore leads to the conclusion that the linkage between the *neo*pentyl group and oxygen is maintained throughout both the esterification and the hydrolysis.

4. The most direct method of demonstration has employed isotopically distinguished oxygen. Polanyi and Szabo[9] hydrolysed amyl acetate in alkaline solution using an aqueous medium containing an increased concentration of the oxygen isotope of mass 18. The amyl alcohol produced did not contain any unusual proportion of this isotope, and the oxygen in this alcohol must therefore have come from the ester. More recently a similar demonstration has been given for the acid hydrolysis of methyl hydrogen succinate; again the isotopically distinguished oxygen from the solvent did not appear in the alcohol.[10] The application of this method to an esterification has been made by Roberts and Urey, who esterified benzoic acid with methyl alcohol containing an increased concentration of the heavy oxygen isotope.[11] The heavy oxygen was not found in the water, the oxygen of which must therefore have come from the benzoic acid.

It is generally recognized that the first step in the processes of esterification and hydrolysis must be an addition. Addition products of esters with both acids and bases have been isolated; thus, Maass and McIntosh prepared a compound of ethyl acetate with hydrogen bromide[12] and von Pechmann isolated an addition product from ethyl benzoate and sodium methoxide,[13] while compound formation between esters and acids has been indicated by freezing-point determinations,[14] by partition methods, and by the effect of sulphuric acid upon the products of nitration of ethyl benzoate.[15]

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[6] Prévost, *Ann. Chim.* 1928, **10**, 147; Ingold and Ingold, *J.C.S.* 1932, 756.

[7] Quayle and Norton, *J. Amer. Chem. Soc.* 1940, **62**, 1170.

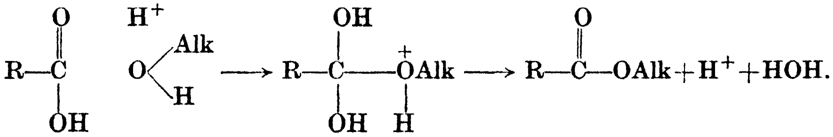
[8] Ibid. 1932, **54**, 3431; 1939, **61**, 1586.

[9] *Trans. Faraday Soc.* 1934, **30**, 508.

[10] Datta, Day, and Ingold, *J.C.S.* 1939, 838.

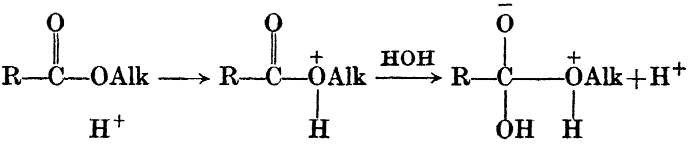
[11] *J. Amer. Chem. Soc.* 1938, **60**, 2391.

Detailed mechanisms for esterification and hydrolysis were put forward by Lowry in 1925.[16] In esterification, according to his views, an addition compound of acid, alcohol, and catalyst is first formed, and from this complex a molecule of water and the catalyst are liberated to give the ester.

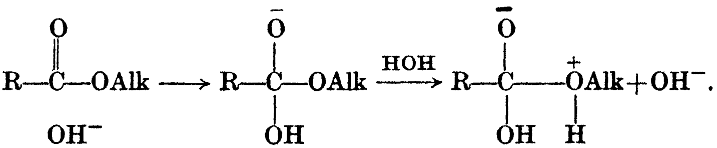

$$\mathrm{R{-}\overset{O}{\overset{\|}{\underset{\underset{OH}{|}}{C}}}\quad \overset{H^+}{O}\!<^{Alk}_{H} \longrightarrow R{-}\overset{OH}{\overset{|}{\underset{\underset{OH}{|}}{C}}}{-}\overset{+}{\underset{\underset{H}{|}}{O}}Alk \longrightarrow R{-}\overset{O}{\overset{\|}{C}}{-}OAlk+H^{+}+HOH.}$$

In hydrolysis, Lowry postulated that addition of proton or hydroxyl ion occurs first, and reaction with a molecule of water then yields the same bipolar ion in each case; this ion then breaks down, giving acid and alcohol.

Acid Hydrolysis


$$\mathrm{\underset{H^+}{R{-}\overset{O}{\overset{\|}{C}}{-}OAlk} \longrightarrow R{-}\overset{O}{\overset{\|}{C}}{-}\overset{+}{\underset{\underset{H}{|}}{O}}Alk \xrightarrow{HOH} R{-}\overset{\bar{O}}{\overset{|}{\underset{\underset{OH}{|}}{C}}}{-}\overset{+}{\underset{\underset{H}{|}}{O}}Alk+H^{+}}$$

Alkaline Hydrolysis


$$\mathrm{\underset{OH^-}{R{-}\overset{O}{\overset{\|}{C}}{-}OAlk} \longrightarrow R{-}\overset{\bar{O}}{\overset{|}{\underset{\underset{OH}{|}}{C}}}{-}OAlk \xrightarrow{HOH} R{-}\overset{\bar{O}}{\overset{|}{\underset{\underset{OH}{|}}{C}}}{-}\overset{+}{\underset{\underset{H}{|}}{O}}Alk+OH^{-}.}$$

Now acid hydrolysis (*b*) is the reverse of esterification (*a*), and a molecule of water is essential to the process. Alkaline hydrolysis (*c*), on the other hand, can be formulated as the reaction of hydroxyl ion with the ester, and water is not necessary in the equation. Moreover, alkaline hydrolysis leads to the salt and not to the acid itself.

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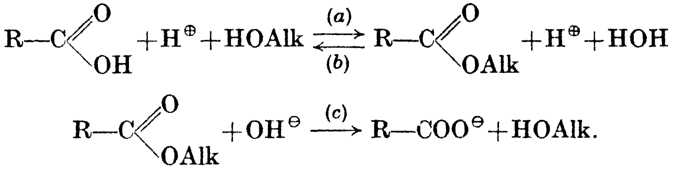
[12] *J. Amer. Chem. Soc.* 1912, **34**, 1273.
[13] *Ber.* 1898, **31**, 503.
[14] Kendall and Booge, *J. Amer. Chem. Soc.* 1916, **38**, 1712.
[15] Baker and Hey, *J.C.S.* 1932, 1226.
[16] Ibid. 1925, **127**, 1380; *Deuxième Conseil de Chimie Solvay*, 1925.



$$\mathrm{R{-}C}\left\langle\begin{matrix}\mathrm{O}\\ \mathrm{OH}\end{matrix}\right. + \mathrm{H}^{\oplus} + \mathrm{HOAlk} \underset{(b)}{\overset{(a)}{\rightleftharpoons}} \mathrm{R{-}C}\left\langle\begin{matrix}\mathrm{O}\\ \mathrm{OAlk}\end{matrix}\right. + \mathrm{H}^{\oplus} + \mathrm{HOH}$$

$$\mathrm{R{-}C}\left\langle\begin{matrix}\mathrm{O}\\ \mathrm{OAlk}\end{matrix}\right. + \mathrm{OH}^{\ominus} \xrightarrow{(c)} \mathrm{R{-}COO}^{\ominus} + \mathrm{HOAlk}.$$

Reference has already been made to the fact that, in the alkaline hydrolysis of a series of substituted ethyl benzoates, the changes in velocity are due entirely (or almost so) to changes in the energy of activation, the non-exponential term of the equation $k = PZe^{-E/RT}$ remaining practically constant throughout.[17] Further, since electron-attractive groups lower the energy of activation, their main influence must be upon the energy needed to bring up the attacking ion (a process which will clearly be favoured by a deficiency of electrons, see p. 41). This has recently been demonstrated more fully by Jenkins,[18] who finds that the plot of the values of E against the electrostatic potential due to the substituent at the carbon atom to which the ester grouping is linked is a straight line of slope approximately Ne (where N is the Avogadro number and e is the electronic charge), a quantity which expresses the work done in bringing up 1 g.-mol. of the ion through one absolute unit of potential; the changes in E are therefore accounted for almost entirely by differences in the work done in bringing up the hydroxyl ion. With acid hydrolysis and esterification the position is quite different, however. In the acid hydrolysis of a series of ethyl benzoates,[19] and also in the esterification of the corresponding acids,[20] changes in both E and P are found. For esterification the variations of E are small and irregular, but for acid hydrolysis the energy of activation decreases as the substituents become more strongly electron-attractive; the actual values of E are considerably higher (by 5,000 to 7,000 calories) than for the alkaline hydrolysis of the same esters, but they vary in the same order. It must be concluded that, in acid hydrolysis, substituents influence principally the energy needed to link a water molecule at the carbon atom of the ester grouping, and the energy of activation is no doubt used mainly for this purpose. It is quite reasonable to suppose that, in the reverse process of esterification, the energy of activation is principally the energy necessary for attaching an alcohol molecule to the carboxyl group.

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[17] See Chap. V.

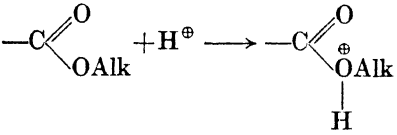
[18] *J.C.S.* 1939, 1780.

[19] Timm and Hinshelwood, *J.C.S.* 1938, 862.

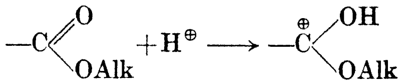
[20] Hartman *et al.*, *J.A.C.S.* 1937, **59**, 2107; 1939, **61**, 2167; 1940, **62**, 1559.

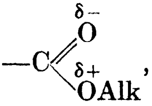
Although, therefore, a molecule of water may be necessary in alkaline hydrolysis (as postulated in the Lowry mechanism), its function must be different from that of the water in acid hydrolysis. It is thus doubtful whether the mechanisms of acid and alkaline hydrolysis can be so similar as are those of Lowry, which ascribe much the same role to the water molecule in both, and lead to the same bipolar complex. It is difficult to understand, moreover, why in acid hydrolysis (but not in esterification) the proton should add at the 'ethereal' oxygen rather than at the 'carbonyl' oxygen, i.e. why the addition of the catalyst should be written as I rather than as II.

I



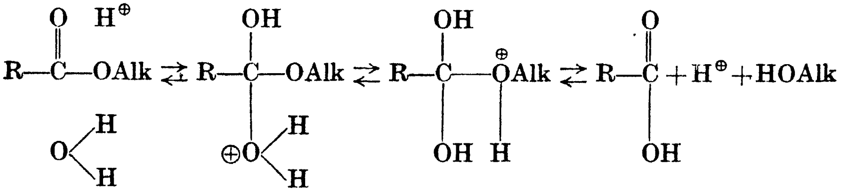
II



The mesomerism of the ester grouping leads to the condition  , and a positive ion is likely to add at the oxygen which is fractionally negative. Finally, it must be remembered that acid and alkaline hydrolysis actually lead to different products—the acid and the anion (salt) respectively.

While, therefore, the Lowry mechanism for esterification appears to be in harmony with the known facts,[21] the following modifications of his hydrolysis mechanisms have much in their favour:[22]

Acid Hydrolysis



(esterification is the reverse of this).

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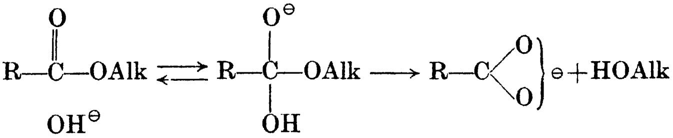
[21] See a critical discussion of mechanisms of esterification, Roberts and Urey, *J. Amer. Chem. Soc.* 1939, **61**, 2584.

[22] See Davies and Evans, *J.C.S.* 1940, 339; Compare Mumm, *Ber.* 1939, **72**, 1874.

Alkaline Hydrolysis



(a water or other solvent molecule may perhaps also be necessary for the removal of energy from the complex).

X

ALIPHATIC SUBSTITUTION

THE term 'substitution' has usually been employed to denote the replacement of hydrogen by some other atom or group, and it was given this conventional but narrow significance in Chapter III. In the wider sense of the word, however, a substitution reaction consists in the replacement of *any* atom or group by *any other*, as in the reactions represented

$$Z+RX = RZ+X$$
$$YZ+RX = RZ+XY$$

and the present chapter deals with substitution processes from this generalized point of view.

Chemical reagents are divisible into two classes, to which Lapworth applied the names 'kationoid' and 'anionoid' respectively. It is probably simplest to describe them as 'electron-seeking' and 'nucleus-seeking', for those of the first class seek a point of the molecule where the electron-availability is high, and those of the second class seek a point where there is a deficiency of electrons. Ingold has introduced the terms 'electrophilic' and 'nucleophilic'.[1] An electrophilic reagent is one which acquires electrons or a share in electrons belonging to some other atom or ion, and a nucleophilic reagent is one which transfers electrons to or shares its electrons with a foreign nucleus.

The reagents which bring about the replacement of hydrogen of the aromatic nucleus are electrophilic,[2] and this is the reason why electron-releasing groups activate the nucleus. The hydroxyl ion is a familiar nucleophilic reagent, and bimolecular alkaline hydrolyses are therefore facilitated by electron-attractive substituents.[3]

It is important to realize that the terms 'electrophilic' and 'nucleophilic' have no reference to the electrical (neutral or charged) condition of the reagent, but exclusively to its electron-accepting or electron-donating capacity. This point will be made clear by an appreciation of the essential similarity of the three processes $NH_3+H^{\oplus} \rightarrow NH_4^{\oplus}$, $BCl_3+NH_3 \rightarrow BCl_3 \cdot NH_3$, and $BF_3+F^{\ominus} \rightarrow BF_4^{\ominus}$. In the first, one of the reagents is charged *positively*, in the second both are *neutral*, while in the last one is a *negative* ion. But the possibility of co-ordination is not connected with these facts; it depends solely upon the ability, in each case, of one reagent to provide electrons and of the other to accept them.[4]

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[1] *J.C.S.* 1933, 1121 (footnote); *Chem. Reviews*, 1934, **15**, 265.

[2] See p. 38.

[3] See p. 41.

Substitution by electrophilic and nucleophilic reagents may be represented by the following general equations, where the processes are denoted by S_E and S_N respectively, and the dotted lines indicate the fate of the electron pairs originally forming the covalent bonds which are broken.

Electrophilic Substitution

$$\left.\begin{array}{r}
Z + R-\vdots X \longrightarrow R-Z + X \\
Y-\vdots Z + R-\vdots X \longrightarrow R-Z + Y-X
\end{array}\right\} \;.\;\;.\;\; S_E$$

Nucleophilic Substitution

$$\left.\begin{array}{r}
Z + R\vdots-X \longrightarrow R-Z + X \\
Y\vdots-Z + R\vdots-X \longrightarrow R-Z + Y-X
\end{array}\right\} \;.\;\;.\;\; S_N$$

Reference has already been made to the modern view of the mechanism of a bimolecular substitution.[5] The process involves the addition of one group and the removal of another, and these are regarded as occurring simultaneously. Thus, in the reaction $Z+RX = RZ+X$, the attacking reagent Z approaches the molecule RX along the line of its axis and on the side of R remote from X, and simultaneously X recedes. The formation of the transition complex thus involves both the bringing up of the reagent and the stretching of the bond which is to be broken.

In recent years, Ingold and Hughes have suggested and found abundant evidence for the existence of another mechanism of substitution, in which the removal and addition processes are not simultaneous, but the slow removal of X is followed by the rapid addition of Z.[6] Such a mechanism is not possible when the group is held very firmly, as in the case of a group linked to the aromatic nucleus, and the theory applies essentially to substitution at a saturated carbon atom (aliphatic substitution). Moreover, it is essential that the energy of dissociation should be reduced by solvation, and so this mechanism is to be anticipated only when the reaction occurs in solution.

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[4] Whereas electrophilic reagents seek the point of a molecule where the electron availability is highest, and nucleophilic reagents that point where it is lowest, there are instances in which *either* of these points may be attacked. A criterion of this type of reaction is that substitution in an aromatic compound is always *op*, whether the directing group be of the *op*-type (when normally all positions are negative but the *o*- and *p*- the most so) or of the *m*-directive type (when all positions are positive but the *o*- and *p*- are most positive). The actual substituting agent is here a free neutral organic radical, and reactions of this kind have been described in Chapter VII (p. 116). The incompleteness of the octet of one carbon atom renders the radical an electrophilic reagent, and the presence of an unshared electron renders it nucleophilic; it thus combines the properties of the two types of reagent (Ingold, *Chem. and Ind.* 1937, **57**, 112).

[5] Chap. V, p. 71.

[6] *J.C.S.* 1935, 244. See also Hughes, *Trans. Faraday Soc.* 1938, **34**, 185.

The view of a dual mechanism applies to substitutions of both the electrophilic and nucleophilic types; the experimental evidence refers, however, to nucleophilic substitution, extensive studies of which have been conducted by Ingold, Hughes, and co-workers.[7] The earliest of these dealt with the decompositions of quaternary ammonium and trialkylsulphonium hydroxides,

$$\mathrm{OH^- + R{-}\overset{+}{N}Alk_3 \longrightarrow R{-}OH + NAlk_3}$$

$$\mathrm{OH^- + R{-}\overset{+}{S}Alk_2 \longrightarrow R{-}OH + SAlk_2},$$

which gave evidence of the existence of two mechanisms,[8] but the most comprehensive investigations are those of the hydrolyses of alkyl halides,

$$\mathrm{OH^- + R{-}X \longrightarrow R{-}OH + X^-}$$

or

$$\mathrm{H{-}OH + R{-}X \longrightarrow R{-}OH + X^- + H^+}.$$

Taking the simplest case, that of a substitution in a 'three-centre system' where only one bond is broken, the two mechanisms of nucleophilic substitution are formulated as follows:

$$\mathrm{Z + R{-}X \longrightarrow R{-}Z + X} \quad .\;.\; \mathrm{S_N2}$$

$$\left.\begin{array}{l} \mathrm{R{-}X \xrightarrow{\text{slow}} R^+ + X} \\ \mathrm{R^+ + Z \xrightarrow{\text{rapid}} R{-}Z} \end{array}\right\} \quad .\;.\; \mathrm{S_N1}$$

For tne hydrolysis of an alkyl halide the mechanisms become

$$\left.\begin{array}{ll} & \mathrm{OH^- + R{-}X \longrightarrow R{-}OH + X^-} \\ \text{or} & \mathrm{H{-}OH + R{-}X \longrightarrow R{-}OH + X^- + H^+} \end{array}\right\} \quad .\;.\; \mathrm{S_N2}$$

$$\left.\begin{array}{ll} & \mathrm{R{-}X \xrightarrow{\text{slow}} R^+ + X^-} \\ \text{followed by} & \mathrm{R^+ + OH^- \xrightarrow{\text{rapid}} R{-}OH} \\ \text{or} & \mathrm{R^+ + H{-}OH \xrightarrow{\text{rapid}} R{-}OH + H^+} \end{array}\right\} \quad .\;.\; \mathrm{S_N1}$$

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[7] This work is described in numerous papers between 1933 and 1940. Only some of the references are given here. A summary with fuller references is found in *Ann. Reports*, 1938 and 1940.

[8] Hughes, Ingold, and Patel, *J.C.S.* 1933, 526; Gleave, Hughes, and Ingold, ibid. 1935, 236.

It is clear that the mechanism denoted S_N2 is bimolecular, while that denoted S_N1 is unimolecular; the measured speed in the latter case is that of the ionization of the alkyl halide.

The predominance of one mechanism or the other will be determined, *inter alia*, by the nature of the group R in the halide RX. If R be varied in the direction of increasing electron repulsion, the effect will be to oppose the attack of the reagent which is necessary for mechanism S_N2, and to facilitate the ionization which is the rate-determining stage in the S_N1 mechanism. A sufficiently wide range of variation in the electron repulsion of R would be expected to lead first to a *retardation* of the reaction by mechanism S_N2, and then to a change of mechanism to S_N1 followed by an *increase* of speed. This reversal of the effect of electron repulsion is due, of course, to the fact that in mechanism S_N1 the nucleophilic reagent is not attacking the molecule itself, and the measured speed is that of an ionization which is facilitated by a flow of electrons from R. There will thus be a mechanistic critical point, on either side of which one mechanism predominates, and, except in the neighbourhood of this point, reaction by the other mechanism will be almost negligible.

Phenomena of the kind anticipated on the basis of the above argument have been observed in the hydrolysis of the series of halides in which R is methyl, ethyl, *iso*propyl, and *tert*-butyl. The electron-repulsive character (+I effect) of these groups increases in this order. The hydrolysis of methyl and ethyl halides by alkali in alcohol or aqueous alcohol is a bimolecular reaction, and the ethyl compound reacts less rapidly than the methyl compound. Kinetic measurements of the hydrolysis of *iso*propyl halides in aqueous alcohol show that reaction occurs by both bimolecular and unimolecular mechanisms, the former being slower than the corresponding reaction for an ethyl halide.[9] The hydrolysis of *tert*-butyl halides in aqueous alcohol or aqueous acetone is unimolecular, and the presence or absence of alkali has no influence; the speed is far greater than that for the *iso*propyl halides under the same conditions.[10] Another factor which would be expected to influence the speed of reaction by the unimolecular mechanism is the ionizing power of the medium, and it is found that increase in the water content of the aqueous alcohol used as solvent leads to a marked increase in the speed of hydrolysis; this is in harmony with the view that an ionization process is the stage which governs the velocity. The relative velocities of hydrolysis of the halides here considered are depicted qualitatively in Fig. 15, which is reproduced from the paper by Gleave, Hughes, and Ingold.[8]

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[9] Hughes, Ingold, and Shapiro, ibid. 1936, 225; 1937, 1177. The velocity coefficients had here to be corrected for some propylene formed simultaneously with the *iso*propyl alcohol.

[10] Hughes, *J.C.S.* 1935, 255; Cooper and Hughes, ibid. 1937, 1183.

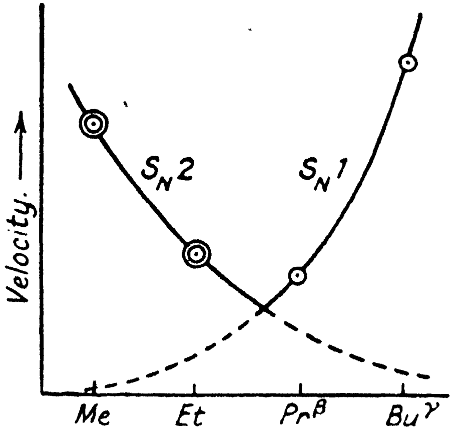

FIG. 15. Velocities of hydrolysis of alkyl halides. (Reproduced from Gleave, Hughes, and Ingold, *J.C.S.* 1935, 238.)

It is found further that other primary alkyl groups give reaction mechanisms of the same type as those established for methyl and ethyl; this is to be expected, since the inductive effects of *n*-alkyl groups do not differ greatly in magnitude from one another. Secondary groups resemble *iso*propyl, and tertiary groups are comparable with *tert*-butyl. The series CH_3, $CH_2(C_6H_5)$, $CH(C_6H_5)_2$, $C(C_6H_5)_3$ is also interesting. While methyl halides are hydrolysed by the bimolecular mechanism, the kinetics of the alkaline hydrolysis of benzyl chloride are of no simple type,[11] benzhydryl halides in aqueous alcohol undergo unimolecular hydrolysis independent of added alkali,[12] and triphenylmethyl halides give conducting solutions in ionizing solvents.[13] It is clear that the hydrolysis of benzyl chloride is on the border-line between the unimolecular and the bimolecular mechanisms, and this explains the fact that alkaline hydrolysis (where the bimolecular mechanism is favoured by a relatively high concentration of OH ions) is accelerated by electron-attractive sub-

[11] Olivier and Weber, *Rec. trav. chim.* 1934, **53,** 869.
[12] Ward *J.C.S.* 1927, 2285.
[13] See Chap. VII, p. 108.

stituents in the nucleus, whereas in absence of alkali (where conditions are less favourable to the bimolecular mechanism) these substituents cause a decrease of speed. Benzylidene chloride and benzotrichloride both undergo unimolecular hydrolysis.[11]

It must be emphasized that the constancy of the first-order velocity coefficients obtained when *tert*-butyl chloride reacts with aqueous alcohol does not give proof of the unimolecular mechanism. In this medium the alkyl halide undergoes two reactions, hydrolysis and alcoholysis,

$$C_4H_9Cl + HOH \longrightarrow C_4H_9OH + HCl$$

$$C_4H_9Cl + HOC_2H_5 \longrightarrow C_4H_9OC_2H_5 + HCl,$$

and both the water and the alcohol are present in such excess that their concentrations do not change perceptibly. The reaction is inevitably of the first order, for a bimolecular reaction under these conditions becomes pseudo-unimolecular. The original demonstration of the unimolecular mechanism depended mainly upon the observation that added hydroxyl ions had no influence on the velocity; if the reaction proceeded by the bimolecular mechanism, the more powerful nucleophilic reagent would give a higher velocity. If the order of the reaction is to provide evidence of mechanism, both reagents must be present at relatively low concentration, and this condition is fulfilled in the kinetic measurements of Bateman and Hughes, where *tert*-butyl chloride was caused to react with small quantities of water in formic acid medium.[14] The high ionizing power of this solvent is favourable to a reaction by the unimolecular mechanism, and, moreover, is not likely to be changed appreciably by the addition of small proportions of water. The hydrolysis is reversible, of course, and under these conditions the back reaction will interfere with the measured speed at a relatively early stage. The results showed, however, that before the reversed reaction becomes perceptible the velocity is independent of the concentration of water, i.e. the hydrolysis is unimolecular; moreover, constant values of the velocity coefficient were obtained for the whole reaction by use of the appropriate expression for a first-order reaction with a second-order reversed change. In contrast with these results for *tert*-butyl chloride, the velocity of hydrolysis of *n*-butyl bromide in formic acid solution increases linearly with the concentration of water.[15] An extension of this work has given the order of velocities methyl < ethyl < *iso*propyl < *tert*-butyl for the hydrolyses of these halides in formic acid medium;[16] this is the order which would be anticipated for the unimolecular mechanism (the velocity of ionization increasing with the electron-repulsive character of the alkyl group), and it shows that, under very favourable conditions, all the halides may be hydrolysed, very largely at least, by this mechanism.

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[14] *J.C.S.* 1937, 1187; 1940, 935.

This direct demonstration of the operation of the unimolecular mechanism in hydrolyses where both reagents are present at small and controllable concentration has been followed by a more definite proof of the same mechanism in cases where one reagent is the solvent (and therefore present in large excess). It has been pointed out above that the original demonstration of the unimolecular character of the hydrolysis of *tert*-butyl chloride in aqueous alcohol or aqueous acetone was found in the observed indifference of the reaction to alkalis, and a mechanism dependent upon ionization was further indicated by the effect of varying the proportion of water in the medium. The more rapid hydrolysis of *tert*-butyl than of *iso*propyl halides pointed to the same conclusion, and later a stereochemical criterion was devised.[17] Recent developments of the work on 'solvolytic' substitutions have made possible a direct kinetic proof of the unimolecular mechanism, which is further confirmed by studies of reaction products.[18]

The hydrolysis of an alkyl halide by the unimolecular mechanism may be represented[19]

$$RX \underset{(2)}{\overset{(1)}{\rightleftarrows}} R^+ + X^- \xrightarrow[(3)]{HOH} ROH + H^+ + X^-.$$

The first (measurable) stage is reversible, and if the velocity of reaction (2) is appreciable in comparison with that of reaction (3), the accumulation of halide ions as the change proceeds will render reaction (2) progressively more important, and will thus reduce the measured velocity (which is the rate at which hydrogen or halide ions increase in concentration). No such retardation will be found in a reaction by the bimolecular mechanism, which will proceed (in presence of excess of water) at a steady first-order rate. Moreover, addition of ions identical with those given by the alkyl halide will similarly decrease the speed of a reaction by the unimolecular mechanism, but again will not influence one by the bimolecular mechanism. In addition to this 'mass-law effect', there is a further source of deviation from strictly first-order kinetics when the unimolecular mechanism is operative; this arises from the increasing ionic strength of the solution as substitution proceeds, and it will lead to a steady *rise* of the first-order coefficient. Addition of an ionized salt leads to an increased speed for the same reason. The combination of mass-law and ionic strength effects has been observed in the solvolytic reactions of *tert*-butyl, benzhydryl [$(C_6H_5)_2CHX$], *p*-alkylbenzhydryl, and *pp'*-dialkylbenzhydryl halides in aqueous acetone, and the results have been shown to be quantitatively in harmony with theoretical predictions based upon the requirements of the unimolecular mechanism. Details cannot be given here, but it may be said that this recent work has given a direct kinetic proof of the operation of the unimolecular mechanism in solvolytic reactions.

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[15] *J.C.S.* 1940, 940.

[16] Ibid., p. 945.

[17] See Chap. XV.

[18] Bateman, Church, Hughes, Ingold, and Taher, *J.C.S.* 1940, 979, and four preceding papers.

[19] Reaction (3) is here written as irreversible. If a hydrolysis is appreciably reversible under the experimental conditions, the forward reaction can be 'isolated' by application of the appropriate kinetic expression.

Confirmation of the unimolecular character of the solvolytic reactions of *tert*-butyl and some other halides has been obtained by the correlation of reaction speeds with the composition of the product obtained under certain conditions. When an alkyl halide reacts by the unimolecular mechanism, the measured velocity is that of the ionization of the halide, $RX \rightarrow R^+ + X^-$, and this is not influenced by the subsequent fate of the alkyl cation. Now in aqueous alcoholic solution *tert*-butyl chloride undergoes simultaneous hydrolysis and alcoholysis, giving a mixture of *tert*-butyl alcohol and *tert*-butyl ethyl ether. If the mechanism is unimolecular, these products are formed in rapid reactions subsequent to the measurable stage, and there will be no direct connexion between the measured reaction rate and the composition of the product. On the other hand, if the reaction is by the bimolecular mechanism, the products are formed in the stage which governs the measured rate, and their proportions can be calculated by a method which was worked out by Olson and Halford.[20] For a bimolecular reaction, therefore, the products found for different alcohol-water mixtures should be in agreement with the compositions calculated; experiment shows that there is no such agreement, and that no relationship exists between product composition and velocity,[21] a result in agreement with expectations based upon the unimolecular mechanism. Again, *tert*-butyl azide and a number of other alkyl azides are stable in aqueous acetone at 50°, and hence when a *tert*-butyl halide is hydrolysed in this medium in presence of sodium azide two products result, C_4H_9OH and $C_4H_9N_3$. If the reactions of the alkyl halides with water and with the azide ion are bimolecular, there will here also be a simple relationship between product composition and reaction velocity, but no such connexion will exist for a reaction by the unimolecular mechanism. The absence of any relationship has been demonstrated for *tert*-butyl bromide, for *p*-*tert*-butylbenzhydryl chloride, and for *pp'*-dimethylbenzhydryl chloride.[18] If parallel reactions are carried out with two halides having the same alkyl group, however, the unimolecular mechanism requires that the composition of the product should be the same in each case, for the alcohol and the azide are formed from the same alkyl cation,

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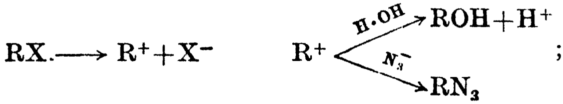
[20] *J. Amer. Chem. Soc.* 1937, 59, 2644.



$$\mathrm{RX} \longrightarrow \mathrm{R^+ + X^-} \qquad \mathrm{R^+} \begin{cases} \xrightarrow{\mathrm{H \cdot OH}} \mathrm{ROH + H^+} \\ \xrightarrow{N_3^-} \mathrm{RN_3} \end{cases} ;$$

this identity of product is not to be expected in the bimolecular mechanism. In the experimental test, products identical within the limits of error were obtained from benzhydryl chloride and benzhydryl bromide in aqueous acetone in presence of sodium azide.[18] Again, therefore, the unimolecular mechanism is indicated.

The results of these detailed investigations of the substitution reactions of alkyl halides leave no doubt regarding the importance of the unimolecular mechanism. The existence of two mechanisms for aliphatic substitution is clearly demonstrated, and the conditions which favour the one or the other have been ascertained.

Nucleophilic substitution in saturated compounds is frequently accompanied by olefin formation, which may be formulated as follows:[22]

$$\mathrm{Z^- + H \vdots\!—CR_2—CR_2\!\vdots—X \longrightarrow Z—H + CR_2{=}CR_2 + X^-}$$

(as before, the dotted lines indicate the fate of the electron pairs forming the covalent bonds that are ruptured). This is a bimolecular mechanism in which a nucleophilic reagent (e.g. hydroxyl ion) extracts a proton simultaneously with the separation of the group X; the proton and X must be linked to adjacent carbon atoms in order that octets may be preserved. Recent work has shown that olefin formation may occur by a unimolecular mechanism, analogous to the S_N1 mechanism for substitution; a slow ionization of X is followed by the rapid removal of the proton. If substitution and olefin formation occur simultaneously, each by a unimolecular mechanism, the rate-controlling process for each is the same, viz. the ionization $RX \rightarrow R^+ + X^-$, but the proportions of olefin and alcohol depend upon subsequent rapid reactions of the organic cation. The total velocity (that of the ionization) will therefore vary with the nature of both R and X in the halide RX, but the relative speeds of substitution and olefin formation are independent of X and depend only upon R. For two halides having the same alkyl group but different halogens (e.g. chloride and bromide), therefore, the differences in velocity should be pronounced, but the relative speeds of olefin formation and hydrolysis should not differ very much. This has been found to be the case for three tertiary chlorides and bromides, thus providing evidence of the unimolecular mechanism of olefin formation.[23] The existence of the two mechanisms, and their dependence upon chemical constitution and physical conditions (solvent, concentration, &c.), account for various apparent discrepancies in the literature.[24]

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[21] Bateman, Hughes, and Ingold, *J.C.S.* 1938, 881.

[22] Hanhart and Ingold, ibid. 1927, 997.

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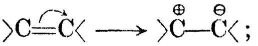
[23] Hughes, Ingold *et al.*, *J.C.S.* 1937, 1277, 1280, 1283.

[24] Ibid. 1940, 899.

XI

ADDITION TO UNSATURATED COMPOUNDS

THE characteristic properties of the olefinic linkage are its capacity for direct addition of reagents such as halogens, halogen hydrides, and sulphuric acid, and its susceptibility to the attack of oxidizing agents. These are, of course, the basis of the familiar qualitative tests with bromine water and alkaline permanganate, while the identification of the products of oxidation or of ozonolysis provides the standard methods for the location of a carbon to carbon double linkage. Lowry suggested in 1923 that the reactions of the four-electron bond are preceded by the electromeric change[1]



$$>C{=}C< \longrightarrow >\overset{\oplus}{C}{-}\overset{\ominus}{C}<;$$

i.e. the molecule is electronically activated and, to use modern terms, takes up or approaches closely to one of the dipolar unperturbed structures. Lowry's view was rendered more probable by the results of an investigation by Norrish of the addition of bromine vapour to ethylene.[2] The reaction occurs entirely at the walls of the containing vessel, and Norrish found that its velocity was dependent upon the chemical nature of the surface. Thus, when the interior of the vessel was coated with different substances, the results shown graphically in Fig. 16 (from Norrish's paper) were obtained; the diminution of pressure, a measure of the extent to which reaction has occurred, is here plotted against time. The speed of addition decreased, with changing surface of the vessel, in the order stearic acid > glass > cetyl alcohol > paraffin wax, i.e. with decrease in the polar character of the surface, the last-named substance slowing it down to about one-seventeenth of its value in an untreated glass vessel. It would appear, therefore, that the effect of the wall is to catalyse some electronic transference such as that postulated by Lowry. Moreover, Davis found that the reaction of bromine with ethylene in pure, dry carbon tetrachloride in the dark is very slow, requiring hours or even days for completion, but is greatly accelerated by small quantities of moisture or by illumination.[3] Some type of activation of the olefin is again indicated.

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[1] See Chap. VI, p. 86.

[2] *J.C.S.* 1923, **123**, 3006.

[3] *J. Amer. Chem. Soc.* 1928, **50**, 2769.

The same conclusion is reached by a different line of argument. The reagents which normally form addition products at an olefinic linkage are of the electrophilic type.[4] This is emphasized by the demonstration that, on treatment of ethylene with bromine water containing sodium chloride or nitrate, the addition products $CH_2Br \cdot CH_2Cl$ or $CH_2Br \cdot CH_2ONO_2$ are formed in addition to $CH_2Br \cdot CH_2Br$.[5] Clearly, one atom of bromine adds initially, the remainder of the halogen molecule appearing (in a dissociating solvent) as *anion*, with which other anions can compete in the second stage of the addition process; the formation of ethylene dibromide under these conditions is thus to be represented as follows:

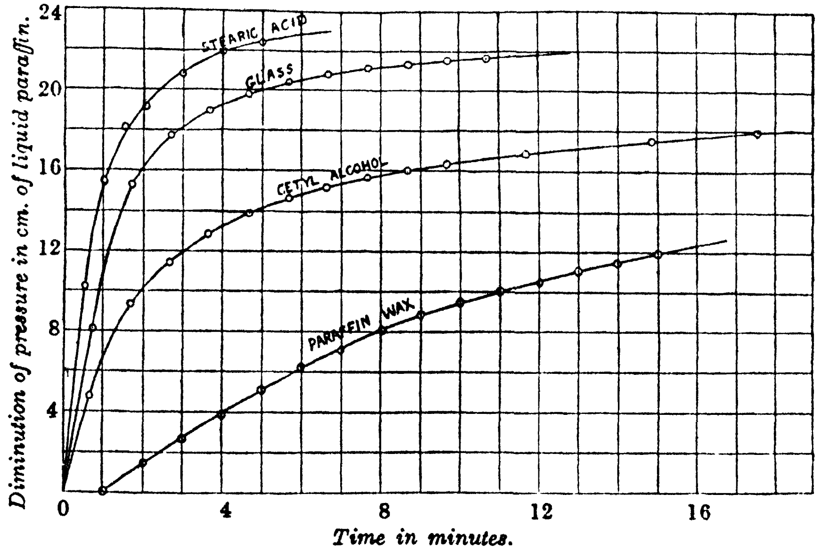

FIG. 16. Effect of the surface of the containing vessel upon the velocity of addition of bromine vapour to ethylene. (Reproduced from Norrish, *J.C.S.* 1923, **123**, 3014.)

$$CH_2{=}CH_2 + Br{-}Br \longrightarrow CH_2Br{-}CH_2^{\oplus} + Br^{\ominus} \longrightarrow CH_2Br{-}CH_2Br.^{6}$$

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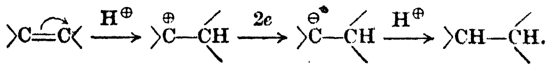
[4] See p. 132.

[5] Francis, *J. Amer. Chem. Soc.* 1925, **47**, 2344.

[6] Burton and Ingold, *J.C.S.* 1928, 912. For the special case of the *reduction* of olefinic compounds (e.g. by sodium amalgam in an aqueous medium), they suggest (ibid. 1929, 2022) a mechanism of the following type:



$$>C{=}C< \xrightarrow{H^{\oplus}} >\overset{\oplus}{C}{-}CH< \xrightarrow{2e} >\overset{\ominus}{C}{-}CH< \xrightarrow{H^{\oplus}} >CH{-}CH<.$$

Unshared electrons are therefore necessary for the formation of the initial covalent bond with bromine, and these can be provided only by means of the mechanism postulated by Lowry, which must either precede or occur simultaneously with the addition; '$\mathrm{C}\underline{\rightarrow}\mathrm{C}$ is not enough; it must be $\mathrm{C}\overset{\curvearrowright}{=}\mathrm{C}$ in which electrons actually dissociate themselves from one of the carbon atoms and become free to be shared with external atoms'.[7]

It is inevitable that the nature of the groups attached to the unsaturated carbon atoms should exert an important influence upon the velocities of addition processes, and this aspect of the subject has been studied by Ingold and Ingold.[8] They point out that a group such as methyl will facilitate the reaction by increasing the electron-availability,

$$\mathrm{CH_3}\!\rightarrow\!\mathrm{C}\overset{\curvearrowright}{=}\mathrm{C},$$

while an electron-attractive group (e.g. halogen, carboxyl) will have the opposite influence. This is in harmony with common experience, as instanced by the relative inactivity of αβ-unsaturated acids towards halogens.[9] By means of experiments in which two olefinic compounds (in methylene chloride solution at −35°) were allowed to compete for a limited quantity of bromine, and the mixed product was subsequently analysed, Ingold and Ingold were able to determine the relative speeds of addition. The following are among the values obtained, the rate of addition of bromine to ethylene being taken as unity:

$(\mathrm{CH_3})_2\mathrm{C{=}CH_2}$	5·5	$\mathrm{COOH{\cdot}CH{=}CH_2}$	0·03
$(\mathrm{CH_3})_2\mathrm{C{=}C(CH_3)_2}$	14	$\mathrm{Br{\cdot}CH{=}CH_2}$	0·04.

These are in agreement with expectation. It will be observed that groups which render the benzene nucleus more active towards an electrophilic reagent also activate the olefinic linkage, and vice versa.

Coming now to the *products* of addition to double bonds, it is obvious that a symmetrical olefinic compound can give one product only; e.g. $\mathrm{CH_2{:}CH_2}+\mathrm{HBr}\longrightarrow\mathrm{CH_3{\cdot}CH_2Br}$. The same remark applies to an unsymmetrical compound if the reagent is symmetrical;

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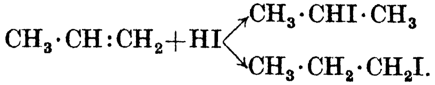
[7] Robinson, *Outline of an Electrochemical Theory of the Course of Organic Reactions* (Institute of Chemistry, 1932), p. 16.

[8] *J.C.S.* 1931, 2354. See also Bauer, *Ber.* 1904, **37**, 3317; 1907, **40**, 918.

[9] See, for example, Sudborough and Thomas, *J.C.S.* 1910, **97**, 715. This has been made the basis of a method of quantitative analysis of a mixture of αβ- and βγ-unsaturated acids (Linstead, *J.C.S.* 1927, 355, 2565).

e.g. $CH_3\cdot CH:CH_2+Br_2 \longrightarrow CH_3\cdot CHBr\cdot CH_2Br$. If, however, both the compound and the reagent are unsymmetrical, there are two possibilities; e.g.



$$CH_3\cdot CH:CH_2+HI \begin{cases} \nearrow CH_3\cdot CHI\cdot CH_3 \\ \searrow CH_3\cdot CH_2\cdot CH_2I. \end{cases}$$

The famous orientation rule of Markownikoff[10] states that, in the addition of halogen acid to an olefinic linkage, the halogen becomes attached to the carbon carrying the smaller number of hydrogen atoms; thus the main product of the addition of hydrogen iodide to propylene is *iso*propyl iodide. Michael[11] sought to generalize on the basis of the 'principle of maximum neutralization', according to which the electronegative group of the addendum will become attached to the more electropositive of the unsaturated carbon atoms. It is evident that the orientation, as well as the velocity of the addition, may be affected by neighbouring groups by reason of their influence upon the electrons of the double bond;[12] thus, in the compound $CHR{=}CHR'$, either of the polarizations $CHR\overset{\curvearrowright}{=}CHR'$ or $\overset{\curvearrowleft}{CHR{=}}CHR'$ may be favoured by the groups R and R′. For example, in acrylic and vinylacetic acids the bromine of hydrogen bromide adds at the β- and γ-positions respectively, owing to the effect of the carboxyl group, although this is contrary to the Markownikoff rule:

$$CH_2:CH\cdot COOH+HBr \longrightarrow CH_2Br\cdot CH_2\cdot COOH$$
$$CH_2:CH\cdot CH_2\cdot COOH+HBr \longrightarrow CH_2Br\cdot CH_2\cdot CH_2\cdot COOH.$$

External factors such as medium, temperature, and illumination may also play a part.[13]

✓Recent investigations by Kharasch and his collaborators have done much to explain the lack of consistency in the recorded experimental observations. In a series of studies of the addition of halogen hydrides to olefinic compounds, they have discovered an important 'peroxide effect'✗They first examined the addition of hydrogen bromide to allyl bromide,[14] where the possible products are 1: 2-dibromopropane and 1 : 3-dibromopropane:

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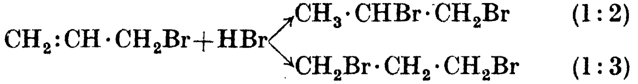
[10] *Annalen*, 1870, **153**, 256.

[11] *J. pr. Chem.* 1899, **60**, 341; *Ber.* 1906, **39**, 2138.

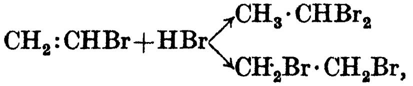
[12] This feature has been considered by Lucas and his co-workers, *J. Amer. Chem. Soc.* 1924, **46**, 2475; 1925, **47**, 1459, and by Kharasch and Darkis, *Chem. Reviews*, 1928, **5**, 571.

[13] See Ipatieff, *Ber.* 1903, **36**, 1988; Ingold and Ramsden, *J.C.S.* 1931, 2746; Boorman, Linstead, and Rydon, ibid. 1933, 568; Sherrill, Mayer, and Walter, *J. Amer. Chem. Soc.* 1934, **56**, 928.



$$CH_2{:}CH\cdot CH_2Br + HBr \begin{array}{lr} \nearrow CH_3\cdot CHBr\cdot CH_2Br & (1:2) \\ \searrow CH_2Br\cdot CH_2\cdot CH_2Br & (1:3) \end{array}$$

Samples of allyl bromide which had been exposed to air were found to contain peroxidic impurities, which could be recognized by their oxidizing action upon ferrous salts; hydrogen bromide added rapidly to these specimens to give mainly 1 : 3-dibromopropane. On the other hand, if peroxides were completely removed and the addition carried out in absence of air, a slow reaction occurred and 80 per cent. of the product was the 1 : 2-dibromide. When oxygen was bubbled through a peroxide-free specimen for ten minutes, the reaction was again rapid and 70 per cent. of the addition compound was 1 : 3-dibromopropane; passage of hydrogen, nitrogen, nitric oxide, or nitrogen peroxide had no such effect. In presence of an 'antioxidant' such as diphenylamine, hydroquinone, thiophenol, or thiocresol, all specimens under all conditions gave 1 : 2-dibromopropane in nearly theoretical yield. In five hundred experiments there was no difference between the behaviour of a peroxide-free specimen and that of one which contained an antioxidant. Kharasch therefore concludes that the 'normal' reaction of allyl bromide with hydrogen bromide produces 1 : 2-dibromopropane, the 1 : 3-dibromide being the result of an 'abnormal' addition catalysed by peroxides; he further expresses the opinion that 'unless conditions are attained which eliminate this oxygen or peroxide effect, no statement as to the direction of addition of hydrogen bromide to a sample of allyl bromide, the peroxide content of which is unknown, is of significance'. Vinyl bromide, which can give either ethylidene dibromide or ethylene dibromide,



$$CH_2{:}CHBr + HBr \begin{array}{l} \nearrow CH_3\cdot CHBr_2 \\ \searrow CH_2Br\cdot CH_2Br, \end{array}$$

is still more sensitive to the presence of peroxides.[15] The 'normal' reaction leads to ethylidene dibromide, and its speed is about one-tenth of that of the peroxide-catalysed addition producing ethylene dibromide. The presence of an antioxidant is necessary in order to obtain the 'normal' product. Similar remarks apply to vinyl chloride.[16] Propylene, α- and *iso*-butylenes, and α-amylene are less sensitive,[17] and give the 'normal' products unless a peroxide (such as benzoyl peroxide) is introduced, when the addition is reversed. The 'normal' products are in accordance with Markownikoff's Rule, viz. $CH_3{\cdot}CHBr{\cdot}CH_3$, $CH_3{\cdot}CH_2{\cdot}CHBr{\cdot}CH_3$, $(CH_3)_2{\cdot}CBr{\cdot}CH_3$, and $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHBr{\cdot}CH_3$ respectively. Kharasch considers the peroxide effect to be responsible for many of the conflicting results recorded in the literature, and he believes that variations in the products with changing external conditions (temperature, medium, illumination) are due to the different effects of the conditions upon the velocities of the normal and peroxide-catalysed reactions.[18] The addition of hydrogen iodide always leads to the 'normal' product, even if peroxides are introduced; nor is there any recorded example of a 'peroxide effect' in the slow addition of hydrogen chloride to double bonds.

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[14] Kharasch and Mayo, *J. Amer. Chem. Soc.* 1933, **55**, 2468.

[15] Kharasch *et al.*, ibid. 1933, **55**, 2521.

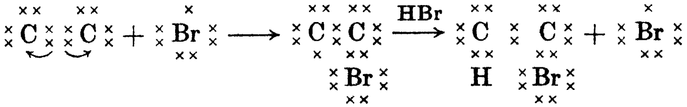
[16] Ibid. 1934, **56**, 712.

A large number of papers dealing with the effects of oxygen and peroxides upon additions to olefinic linkages and upon certain other reactions have appeared during the past few years. The literature has been summarized by Smith in three articles, where full references may be found, and to which the reader is referred.[19]

The 'normal' addition of hydrogen bromide to an olefinic compound may be formulated:

$$>\!\mathrm{C}{=}\mathrm{C}\!< + \mathrm{HBr} \longrightarrow\ >\!\mathrm{CH}{-}\overset{+}{\mathrm{C}}\!< + \mathrm{Br}^- \longrightarrow\ >\!\mathrm{CH}{-}\mathrm{CBr}.$$

Kharasch considers that the peroxide-catalysed 'abnormal' addition is initiated by bromine *atoms* liberated from the hydrogen bromide, and that a chain reaction is set up in some such way as indicated by the following electronic representation:



$$\overset{\times\times}{\mathrm{C}}\,\overset{\times\times}{\mathrm{C}} + \overset{\times}{\underset{\times\times}{\mathrm{Br}}} \longrightarrow \underset{\underset{\times\times}{\mathrm{Br}}}{\overset{\times\times}{\mathrm{C}}}\,\overset{\times\times}{\underset{\times\times}{\mathrm{C}}} \xrightarrow{\mathrm{HBr}} \underset{\mathrm{H}}{\overset{\times\times}{\underset{\times\times}{\mathrm{C}}}}\;\underset{\underset{\times\times}{\mathrm{Br}}}{\overset{\times\times}{\underset{\times\times}{\mathrm{C}}}} + \overset{\times}{\underset{\times\times}{\mathrm{Br}}}$$

Addition to Conjugated Systems. Numerous observations of the addition of bromine to butadiene and its derivatives, which contain two olefinic linkages separated by a single bond ('conjugated' double linkages), have indicated that the principal product is usually the 1 : 4 (terminal) dibromide:

$$CH_2{=}CH{-}CH{=}CH_2 + Br_2 \longrightarrow CH_2Br{-}CH{=}CH{-}CH_2Br.$$

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[17] Ibid. 1933, **55**, 2531; 1934, **56**, 1212, 1243, 1642.

[18] Ibid. 1936, **58**, 57.

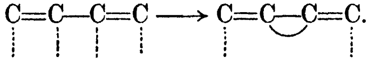
[19] *Chem. and Ind.* 1937, **56**, 833; 1938, **57**, 461; *Ann. Reports*, 1939, **36**, 219.

Recent investigations confirm the predominance of this type of addition. Thus, Farmer, Lawrence, and Thorpe find the following percentages of the terminal dibromide in the product of addition of bromine to butadiene in different solvents:[20]

Solvent	*Temperature*	*Per cent. 1 : 4*
Acetic acid	4°	70
Carbon disulphide	−15°	66
Chloroform	−15°	63
Hexane	−15°	38

The terminal dibromide has also been found in major quantity when bromine is added to $\alpha\delta$-, $\alpha\gamma$-, and $\beta\gamma$-dimethylbutadienes[21] and to isoprene.[22] Muconic acid and $\alpha\delta$-diphenylbutadiene, however, give 1 : 2 addition of bromine but 1 : 4 addition of hydrogen.[23]

Thiele's Theory of Partial Valencies[24] was an attempt to interpret 1 : 4 addition. The reactivity of the olefinic linkage was attributed to the incomplete saturation of the affinities of the doubly bound carbon atoms, which were thus regarded as possessing free 'partial valencies' (an application of Werner's conception of 'residual affinity'). In the case of a compound such as butadiene, the partial valencies of the central carbon atoms might then neutralize each other by 'conjugation', leaving free partial valencies only at the terminal atoms:



$$C{=}C{-}C{=}C \longrightarrow C{=}C{-}C{=}C.$$

All cases of 1 : 2 addition to compounds of the butadiene type formed exceptions to Thiele's theory, and various ingenious interpretations were suggested to account for them. The theory immediately met with violent criticism,[25] and it was clearly incapable of embracing even a majority of the experimental observations.

In 1922 Gillet suggested[26] that 1 : 2 addition always occurred first, and might be followed by migration of halogen to the 4-position by what is now known as an 'anionotropic' change.[27] The work of Farmer, Lawrence, and Thorpe[20] showed, however, that this change, while it can occur, is far too slow to account for the high proportion of the 1 : 4 derivative in the product. Accordingly, Burton and Ingold modified Gillet's mechanism.[28] Starting from Francis's demonstration that one atom of halogen adds initially,[29] they suggested a scheme of the following type for the addition of bromine to conjugated double bonds under conditions which permit ionization. The olefinic compound first adds one bromine,

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[20] *J.C.S.* 1928, 729.

[21] Farmer, Lawrence, and Scott, ibid. 1930, 510.

[22] Staudinger *et al.*, *Helv. Chim. Acta*, 1922, **5**, 756.

[23] Strauss, *Ber.* 1909, **42**, 2866; Chandrasena and Ingold, *J.C.S.* 1922, **121**, 1306.

[24] *Annalen*, 1899, **306**, 87. Thiele's application of his theory to benzene is well known.

[25] Michael, *J. pr. Chem.* 1899, **60**, 467; Erlenmeyer, *Annalen*, 1901, **316**, 43; Hinrichsen, ibid. 1904, **336**, 168. The presence of the 1 : 2 dibromide in the product of addition of bromine to butadiene, originally claimed by Griner (*Compt. rend.* 1893, **116**, 723; **117**, 553) was later admitted by Thiele himself (see Strauss, *Ber.* 1909, **42**, 2872).

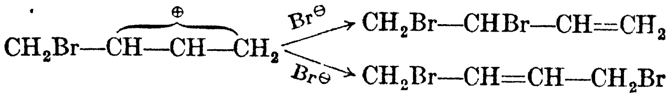
[26] *Bull. Soc. Chim. Belg.* 1922, **31**, 365. See also *Bull. Soc. Chim.* 1927, **41**, 927. Compare Prévost, *Compt. rend.* 1927, **185**, 132.

$$CH_2\overset{\backprime}{=}CH—CH=CH_2+Br_2 \longrightarrow CH_2Br—\check{C}H—CH=CH_2+Br^{\ominus}.$$

The resulting positive ion is a mesomeric structure, and the charge will be distributed in accordance with the formulation

$$CH_2Br—\acute{C}H—CH—\grave{C}H_2.$$

Addition of a bromide ion can therefore occur in such a way as to give the 1 : 2-dibromide or to give the 1 : 4-dibromide,



$$CH_2Br—\overset{\oplus}{\overbrace{CH—CH—CH_2}} \begin{cases} \xrightarrow{Br^{\ominus}} CH_2Br—CHBr—CH=CH_2 \\ \xrightarrow{Br^{\ominus}} CH_2Br—CH=CH—CH_2Br \end{cases}$$

and, provided the medium permits the initial ionization, the proportions of the dibromides formed will depend upon their relative stabilities.[30] On the other hand, in a non-ionizing solvent such as hexane the dissociation will presumably not be possible. The attack of the second bromine will commence while it is still attached to the first, and the complex thus formed, of the type $\begin{matrix} Br—Br \\ \uparrow \quad \downarrow \\ C\sim\sim C \end{matrix}$, will be that which leads to a ring with the minimum of strain. The results of Farmer, Lawrence, and Thorpe point to the preferential formation of the 1 : 2-dibromide under these conditions.[31]

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[27] See Chap. XII, p. 177.

[28] *J.C.S.* 1928, 910; Ingold, *Ann. Reports*, 1928, **25**, 131.

[29] See p. 143.

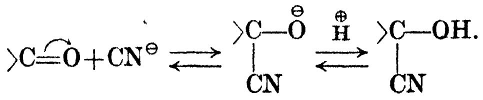
[30] The preponderance of one isomeride when addition of bromine occurs, and of the other when hydrogen is added (e.g. in muconic acid or αδ-diphenylbutadiene) is due to the different mechanisms involved. The mesomeric ion is positive and negative respectively (see ref. 6), and hence groups have opposite effects.

[31] The above suggestions were made to the author by Professor Ingold in a private communication (October 1936).

Addition of Nucleophilic Reagents. The olefinic linkage forms addition products with a whole group of electrophilic reagents such as halogens and halogen hydrides; the carbonyl bond $>C=O$, on the other hand, exhibits reactivity towards a quite distinct group of substances, typified by hydrogen cyanide and sodium bisulphite, which do not normally add to olefinic compounds. In these addition reactions of the carbonyl group, hydrogen always becomes linked to oxygen and the anionic portion of the reagent to carbon.[32] The natural inference is that, in its addition reactions, the carbon to oxygen double bond is polarized in the direction $>C\overset{\curvearrowright}{=}O$; indeed, the energy of formation of the carbonyl group indicates resonance between $>C=O$ and $>\overset{\oplus}{C}-\overset{\ominus}{O}$,[33] and the existence of a permanent dipole is demonstrated by the high electric moments of ketones and aldehydes (of the order 2·8 D).

Lapworth's observations of the effects of acids, alkalis, and alkaline cyanides upon the addition of hydrocyanic acid to ketones have shown that the initial stage in the process is the relatively slow co-ordination of cyanide ion to produce the complex anion $>C(CN)\overset{\ominus}{O}$, this being followed by instantaneous combination with hydrogen ion to give the cyanohydrin.[34] This view of the reaction, which ascribes to cyanohydrins the characters of weak acids, was confirmed by the isolation of crystalline products (salts) by the action of potassium cyanide upon benzaldehyde and camphorquinone.[35] The distinction between the additive reactions of the olefinic linkage and those of the carbonyl bond now becomes clear; the former adds electrophilic reagents, and the latter nucleophilic reagents.

Since the covalency of carbon is limited to four, the addition of the cyanide ion to carbonyl carbon must be accompanied by the *complete* transfer of a pair of electrons to the sole control of oxygen, and the mechanism of cyanohydrin formation is therefore



$$>C\overset{\curvearrowright}{=}O+CN^{\ominus} \rightleftharpoons \begin{array}{l}>C-\overset{\ominus}{O}\\ \quad |\\ \quad CN\end{array} \overset{\overset{\oplus}{H}}{\rightleftharpoons} \begin{array}{l}>C-OH.\\ \quad |\\ \quad CN\end{array}$$

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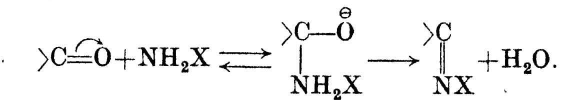
[32] Similarly, in reactions with metal alkyls and Grignard reagents, and in the Reformatzky reaction, the metal becomes linked to oxygen and an alkyl group to carbon.

[33] Pauling and Sherman, *J. Chem. Physics*, 1933, **1**, 606.

[34] *J.C.S.* 1903, **83**, 995.

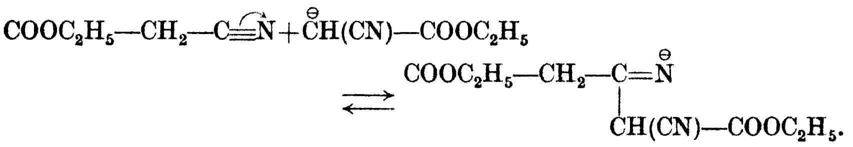
[35] Ibid. 1904, **85**, 1206.

This is no doubt typical of the manner in which addition products are normally formed by the carbonyl group. The process is reversible, and Lapworth and Manske have determined the equilibrium constants for a considerable number of cyanohydrins;[36] reversibility appears, indeed, to be a characteristic of the additions of nucleophilic reagents to unsaturated systems. The production of compounds such as oximes and hydrazones is doubtless to be included among addition reactions,[37] the second stage (not reversible) now being the elimination of the elements of water, accompanied by a readjustment of covalencies,



$$>C{=}O + NH_2X \rightleftharpoons \begin{array}{l} >C-\overset{\ominus}{O} \\ \quad | \\ \quad NH_2X \end{array} \longrightarrow \begin{array}{l} >C \\ \quad \| \\ \quad NX \end{array} + H_2O.$$

Further, the addition of a nucleophilic reagent to the carbon to nitrogen triple linkage (Thorpe Reaction)[38] must involve a process of an exactly similar type, e.g.



$$COOC_2H_5{-}CH_2{-}C{\equiv}N + \overset{\ominus}{C}H(CN){-}COOC_2H_5 \rightleftharpoons \begin{array}{l} COOC_2H_5{-}CH_2{-}C{=}\overset{\ominus}{N} \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\qquad\quad CH(CN){-}COOC_2H_5. \end{array}$$

In a number of instances an *olefinic* linkage exhibits the capacity for addition of nucleophilic reagents.[39] The compounds in which such reactivity is observed are αβ-unsaturated ketones, aldehydes, esters, and nitriles. The olefinic linkage is here far less reactive than normally towards electrophilic reagents,[40] while the carbonyl bond shows a decreased reactivity towards nucleophilic reagents. Lapworth[41] has studied the addition of hydrocyanic acid to the olefinic linkages in phorone, mesityl oxide, and benzylidenebenzyl cyanide, and finds that the conditions which favour the reaction in each case are exactly those which facilitate cyanohydrin formation. The best-known instance of such addition, however, is the Michael Reaction,[42] as exemplified by the addition of ethyl sodio-malonate to cinnamic ester:

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[36] Ibid. 1928, 2533; 1930, 1976.

[37] An addition compound of chloral and hydroxylamine has been isolated by Hantzsch (*Ber.* 1892, **25**, 702).

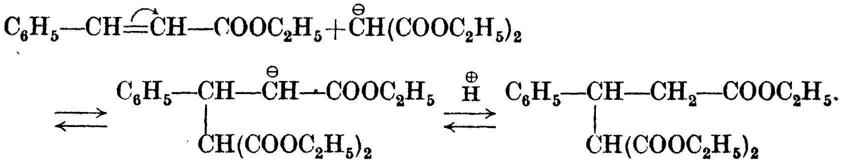
[38] *J.C.S.* 1904, **85**, 1726; 1906, **89**, 1906. The above formulation of the reaction as the addition of the anion of the cyanoacetic ester is justified by the findings of Holden and Lapworth (*J.C.S.* 1931, 2368).

[39] Lapworth, *J.C.S.* 1904, **85**, 1214.

[40] Compare p. 144.

[41] References 34 and 39.

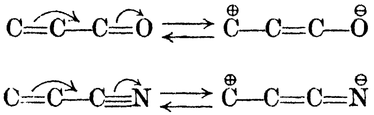
[42] *J. pr. Chem.* 1887, **35**, 349.



$$C_6H_5{-}CH{=}CH{-}COOC_2H_5 + \overset{\ominus}{C}H(COOC_2H_5)_2$$

$$\rightleftarrows \begin{array}{l} C_6H_5{-}CH{-}\overset{\ominus}{C}H{-}COOC_2H_5 \\ \quad | \\ \quad CH(COOC_2H_5)_2 \end{array} \underset{\rightleftarrows}{\overset{\oplus}{H}} \begin{array}{l} C_6H_5{-}CH{-}CH_2{-}COOC_2H_5. \\ \quad | \\ \quad CH(COOC_2H_5)_2 \end{array}$$

It is significant that all compounds in which nucleophilic reagents add to the olefinic linkage contain one of the groupings $C{=}C{-}C{=}O$ or $C{=}C{-}C{\equiv}N$. The electromeric changes



$$C{=}C{-}C{=}O \rightleftarrows \overset{\oplus}{C}{-}C{=}C{-}\overset{\ominus}{O}$$

and

$$C{=}C{-}C{\equiv}N \rightleftarrows \overset{\oplus}{C}{-}C{=}C{=}\overset{\ominus}{N}$$

are here possible, and the compounds are actually mesomeric structures. This accounts for the depression of the *normal* additive reactivity both of carbonyl carbon (which is rendered less susceptible to the attack of a nucleophilic reagent since its deficiency of electrons is supplied from the olefinic linkage) and of the olefinic bond (where the provision of unshared electrons is made more difficult). At the same time, there is provided a point of attack for a nucleophilic reagent at the carbon atom situated in the β-position with respect to the carbonyl or nitrile group,[43] and it is to this carbon that the anion invariably adds.

Catalysed Additions of Nucleophilic Reagents. It remains to consider the large group of reactions in which the addition of a nucleophilic reagent occurs only in presence of a catalyst. In all of these the reagent is a compound possessing 'incipiently ionized' hydrogen, that is, hydrogen which is 'loosened' in such a way that its removal as proton is relatively easy. This condition is brought about by the influence of neighbouring electron-attractive groups.[44] The *catalysed* addition of such a molecule may be distinguished from the *uncatalysed* addition of an anion such as $CN^{\ominus}$ in the examples described above. It may occur at $>C{=}O$ (aldol reaction), and also at $>C{=}C<$ or $-C{\equiv}N$ (analogues of the Michael and Thorpe reactions), when these groups are suitably placed. Like cyanohydrin formation, these additions are reversible.[45]

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[43] Compare Cooper, Ingold, and Ingold, *J.C.S.* 1926, 1868.

[44] Holmes and Ingold, ibid. 1926, 1305. Compare Lapworth, *Mem. Manchester Phil. Soc.* 1920, **64**, No. 3, p. 3; E. H. Ingold, *Chem. and Ind.* 1923, **42**, 1246; Higginbotham and Lapworth, *J.C.S.* 1922, **121**, 2823.

The simplest aldol condensation is that between two molecules of acetaldehyde to give β-hydroxybutaldehyde,

$$CH_3—CHO + HCH_2—CHO \rightleftarrows CH_3—CH(OH)—CH_2—CHO,$$

a product which loses the elements of water with great facility producing crotonaldehyde, $CH_3—CH{=}CH—CHO$. This loss of water is a characteristic of aldols, which as a consequence frequently cannot be isolated.

There can be little doubt that aldol addition is the first step in a number of well-known condensation reactions of carbonyl compounds, including the Claisen reaction (aldehyde+aldehyde or ketone in presence of alkali),[46] the Knoevenagel reaction (aldehyde or ketone+malonic, acetoacetic or cyanoacetic ester or a nitro-compound in presence of an organic base),[47] and the Perkin reaction (aldehyde+acid anhydride in presence of salt).[48] All these reactions may be represented by appropriate modifications of the general scheme

$$\underset{\text{(aldehyde component)}}{R\cdot CHO} + \underset{\text{(second component)}}{CH_2R'R''} \rightarrow R\cdot CH{:}CR'R'' + H_2O$$

where at least one of the groups R′, R″ is of such a character that the methylene group is activated (i.e. the protons are incipiently ionized); for example, in the (Claisen) reaction of benzaldehyde with acetophenone, $R' = CO\cdot C_6H_5$, $R'' = H$; in the reaction of an aldehyde with ethyl malonate (Knoevenagel), $R' = R'' = COOC_2H_5$; and in the Perkin reaction of benzaldehyde with acetic anhydride, $R' = CO\cdot O\cdot COCH_3$, $R'' = H$. In some instances the intermediate aldol has actually been isolated; in certain other cases, where the subsequent loss of water is not possible, no reaction is observed (e.g. between benzophenone and cyanoacetic ester),[49] and this is probably due to the instability of the aldol, the equilibrium favouring the reagents almost entirely.

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[45] Ingold and Perren, *J.C.S.* 1921, **119**, 1582, 1865; E. H. Ingold, ibid. 1923, **123**, 1717; 1924, **125**, 1319.

[46] Claisen, *Ber.* 1881, **14**, 2471.

[47] Knoevenagel, ibid. 1904, **37**, 4461.

[48] Perkin, *J.C.S.* 1877, **32**, 389. Evidence recently summarized by Breslow and Hauser (*J. Amer. Chem. Soc.* 1939, **61**, 786) leads definitely to the conclusion that the aldehyde condenses with the anhydride, the salt acting catalytically. This is in harmony with Perkin's original view, which has been supported by Michael and others, but contrary to the interpretation of the reaction first put forward by Fittig and assumed in most recent writings on the subject (including the first edition of this book). A similar reaction is that of benzaldehyde with ethyl acetate in presence of sodium triphenylmethyl, where the aldol has been isolated (Hauser and Breslow, ibid. p. 793); an aldol has also been prepared from benzaldehyde and ethyl *iso*butyrate.

Comparable with these reactions is the Claisen acetoacetic ester condensation (ester+ester or ketone in presence of sodium ethoxide or some other powerful condensing agent),[50] which may be formulated as follows (COX = COOAlk, COAlk):

$$\underset{\text{(ester component)}}{R\cdot COOAlk}+\underset{\text{(second component)}}{CHR'R''\cdot COX} \rightarrow R\cdot CO\cdot CR'R''\cdot COX+HOAlk.$$

An ester molecule here replaces the aldehyde of the reactions referred to above, and the OAlk group is split off as alcohol.

Ethyl malonate and similar compounds will also add to the $>C=C<$ bond if an organic base is present as catalyst.[47] Hauser and Abramovitch have recently studied the reaction of ethyl acetoacetate with benzylideneacetophenone, and they find further that both ethyl *iso*butyrate and ethyl phenylacetate add to ethyl cinnamate in presence of sodium triphenylmethyl.[51]

The function of the catalyst in these changes has been much discussed. Knoevenagel believed that, in the reaction which bears his name, the organic base reacts initially with the aldehyde. This view was based upon the isolation of products such as $R\cdot CH(OH)\cdot NHR'$, $R\cdot CH(NHR')_2$, and $R\cdot CH(NR'R'')_2$, which undergo reaction with malonic ester and similar compounds.[52] The catalytic effect of tertiary bases here remains unexplained, however, and the fact that the compounds can be isolated is no proof that they are intermediates in the processes under discussion. Some of the earlier mechanisms of the acetoacetic ester condensation similarly postulate an addition complex of ester and ethoxide.[53]

It is now some forty years since Lapworth suggested that, in all these reactions, the catalyst removes incipiently ionized hydrogen from the 'second component', thus giving an anion which forms an aldol addition product with the 'aldehyde component' or 'ester component'.[54] Recent mechanisms[55] have incorporated the essentials of Lapworth's schemes, and the following formulation is of the type now usually accepted. The condensations of aldehydes may be written in general (B represents the catalyst, which is an organic base, ethoxide, hydroxide, acetate, or other anion):

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[49] Haworth, *J.C.S.* 1909, **95**, 480.

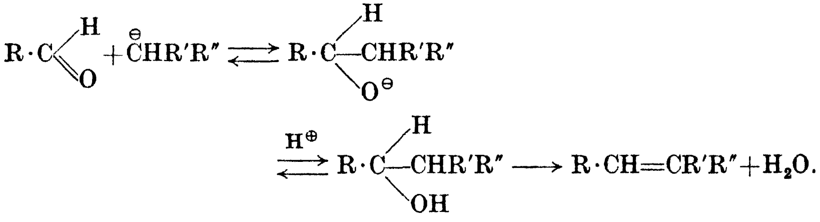
[50] Claisen, *Ber.* 1887, **20**, 646.

[51] *J. Amer. Chem. Soc.* 1940, **62**, 1763.

[52] Knoevenagel, *Ber.* 1898, **31**, 2596. Compare Dimroth and Zoeppritz, ibid. 1902, **35**, 984; Dilthey, ibid. 1929, **62**, 1603, 1609.

[53] Claisen, ref. 50; Dieckmann, *Ber.* 1900, **33**, 2670.

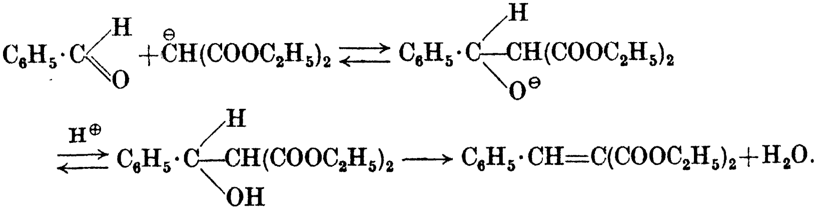
$$B + CH_2R'R'' \rightleftharpoons BH^{\oplus} + \overset{\ominus}{C}HR'R''$$



The following examples will serve to clarify the scheme:

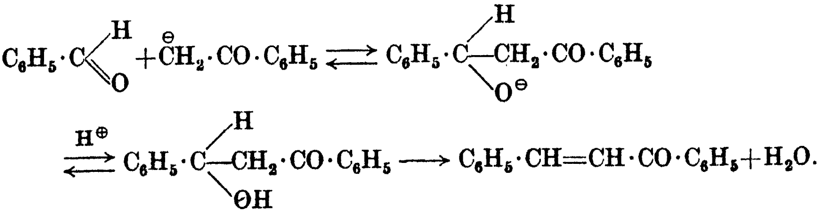
(*a*) The reaction of benzaldehyde with ethyl malonate in presence of piperidine (Knoevenagel) ($R' = R'' = COOC_2H_5$):

$$C_5H_{10}NH + CH_2(COOC_2H_5)_2 \rightleftharpoons C_5H_{10}\overset{\oplus}{N}H_2 + \overset{\ominus}{C}H(COOC_2H_5)_2$$



(*b*) The reaction of benzaldehyde with acetophenone in presence of sodium hydroxide (Claisen) ($R' = CO\cdot C_6H_5$; $R'' = H$):

$$OH^{\ominus} + CH_3\cdot CO\cdot C_6H_5 \rightleftharpoons HOH + \overset{\ominus}{C}H_2\cdot CO\cdot C_6H_5$$



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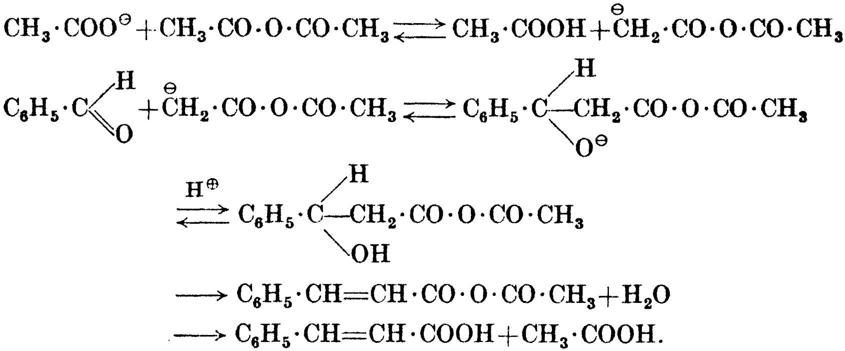
[54] *J.C.S.* 1901, **79**, 1269. Compare Nef, *Annalen*, 1897, **298**, 218; Michael, *Ber.* 1900, **33**, 3731; Hann and Lapworth, *J.C.S.* 1904, **85**, 46.

[55] Arndt and Eistert, *Ber.* 1936, **69**, 2381; Hauser and Renfrow, *J. Amer. Chem. Soc.* 1937, **59**, 1823; 1938, **60**, 463. Hauser, ibid. 1938, **60**, 1957; Hauser and Breslow, ibid. 1939, **61**, 793; 1940, **62**, 593.

(*c*) The reaction of benzaldehyde with acetic anhydride in presence of sodium acetate (Perkin) ($R' = CO\cdot O\cdot COCH_3$; $R'' = H$):



$$\mathrm{CH_3\cdot COO^{\ominus}+CH_3\cdot CO\cdot O\cdot CO\cdot CH_3 \rightleftarrows CH_3\cdot COOH+\overset{\ominus}{C}H_2\cdot CO\cdot O\cdot CO\cdot CH_3}$$

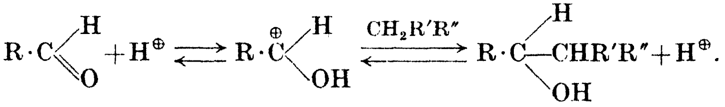
$$\mathrm{C_6H_5\cdot C\Big\langle{}^{H}_{O}+\overset{\ominus}{C}H_2\cdot CO\cdot O\cdot CO\cdot CH_3 \rightleftarrows C_6H_5\cdot \overset{H}{\underset{O^{\ominus}}{C}}-CH_2\cdot CO\cdot O\cdot CO\cdot CH_3}$$

$$\mathrm{\overset{H^{\oplus}}{\rightleftarrows} C_6H_5\cdot \overset{H}{\underset{OH}{C}}-CH_2\cdot CO\cdot O\cdot CO\cdot CH_3}$$

$$\mathrm{\longrightarrow C_6H_5\cdot CH{=}CH\cdot CO\cdot O\cdot CO\cdot CH_3+H_2O}$$

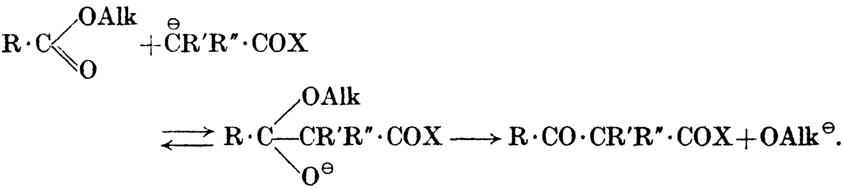
$$\mathrm{\longrightarrow C_6H_5\cdot CH{=}CH\cdot COOH+CH_3\cdot COOH.}$$

Aldol Condensations may also occur under the catalytic influence of an acid, and they are then written as follows:[56]



$$\mathrm{R\cdot C\Big\langle{}^{H}_{O}+H^{\oplus} \rightleftarrows R\cdot \overset{\oplus}{C}\Big\langle{}^{H}_{OH} \overset{CH_2R'R''}{\rightleftarrows} R\cdot \overset{H}{\underset{OH}{C}}-CHR'R''+H^{\oplus}.}$$

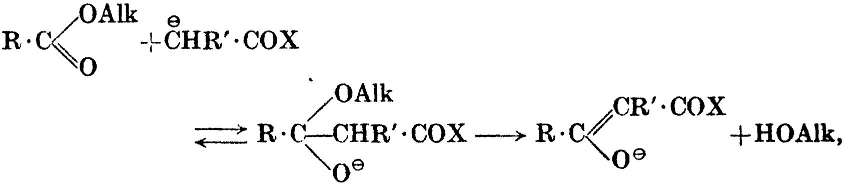
For the Acetoacetic Ester Condensation, where the aldehyde of the above reactions is replaced by an ester, the scheme becomes



$$\mathrm{R\cdot C\Big\langle{}^{OAlk}_{O}+\overset{\ominus}{C}R'R''\cdot COX}$$

$$\mathrm{\rightleftarrows R\cdot \overset{OAlk}{\underset{O^{\ominus}}{C}}-CR'R''\cdot COX \longrightarrow R\cdot CO\cdot CR'R''\cdot COX+OAlk^{\ominus}.}$$

If R″ is hydrogen, as in the more familiar examples of this type of condensation,[57] the product actually formed is the enolate, and the above scheme may be modified as follows:



$$\mathrm{R\cdot C\Big\langle{}^{OAlk}_{O}+\overset{\ominus}{C}HR'\cdot COX}$$

$$\mathrm{\rightleftarrows R\cdot \overset{OAlk}{\underset{O^{\ominus}}{C}}-CHR'\cdot COX \longrightarrow R\cdot C\Big\langle{}^{CR'\cdot COX}_{O^{\ominus}}\;+HOAlk,}$$

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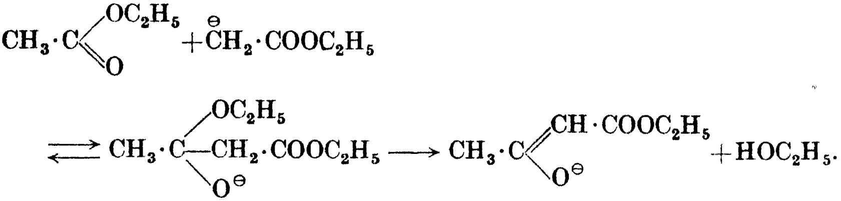
[56] Compare Arndt and Eistert, ref. 55.

[57] The presence of two α-hydrogen atoms in the 'second component' is not essential, as has sometimes been claimed (see Hauser and Renfrow, ref. 55), although this condition is fulfilled in those instances where the condensation proceeds most readily.

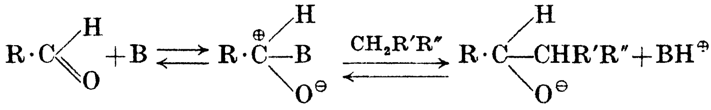
or, to write the actual case of the synthesis of acetoacetic ester itself ($R' = R'' = H$; $COX = COOC_2H_5$):



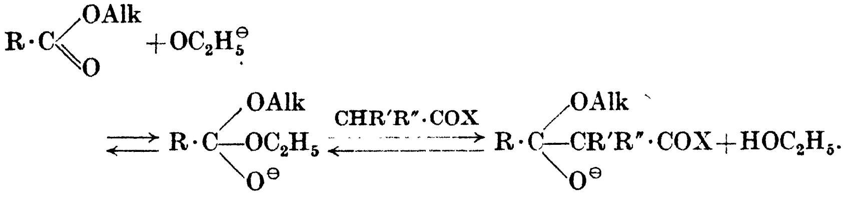
$$CH_3\cdot C\begin{array}{l}\diagup OC_2H_5\\ \diagdown O\end{array} + \overset{\ominus}{C}H_2\cdot COOC_2H_5$$

$$\rightleftarrows CH_3\cdot C\begin{array}{l}\diagup OC_2H_5\\ -CH_2\cdot COOC_2H_5\\ \diagdown O^{\ominus}\end{array} \longrightarrow CH_3\cdot C\begin{array}{l}\diagup CH\cdot COOC_2H_5\\ \diagdown O^{\ominus}\end{array} + HOC_2H_5.$$

In spite of the general acceptance of mechanisms of this type, there is no proof that the only function of the catalyst (or even its main function) is the removal of a proton from the 'second component'. It is quite possible that the most important part played by the catalyst is the activation of the carbonyl group of the aldehyde or ester (probably by conversion of $\rangle C{=}O$ to the dipolar form $\rangle\overset{+}{C}-\overset{-}{O}$), which might be achieved by the formation of an addition complex, as in ester hydrolysis or the cyanohydrin reaction. This energized complex would then react with the 'second component', and the ion of the aldol would be formed according to a scheme of the following type:



$$R\cdot C\begin{array}{l}\diagup H\\ \diagdown O\end{array} + B \rightleftarrows R\cdot \overset{\oplus}{C}\begin{array}{l}\diagup H\\ -B\\ \diagdown O^{\ominus}\end{array} \underset{\longleftarrow}{\xrightarrow{CH_2R'R''}} R\cdot C\begin{array}{l}\diagup H\\ -CHR'R''\\ \diagdown O^{\ominus}\end{array} + BH^{\oplus}$$

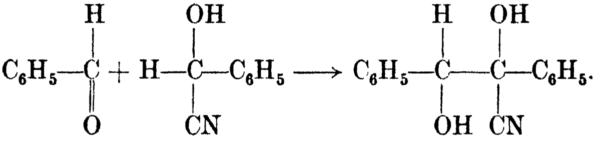


$$R\cdot C\begin{array}{l}\diagup OAlk\\ \diagdown O\end{array} + OC_2H_5^{\ominus}$$

$$\rightleftarrows R\cdot C\begin{array}{l}\diagup OAlk\\ -OC_2H_5\\ \diagdown O^{\ominus}\end{array} \underset{\longleftarrow}{\xrightarrow{CHR'R''\cdot COX}} R\cdot C\begin{array}{l}\diagup OAlk\\ -CR'R''\cdot COX\\ \diagdown O^{\ominus}\end{array} + HOC_2H_5.$$

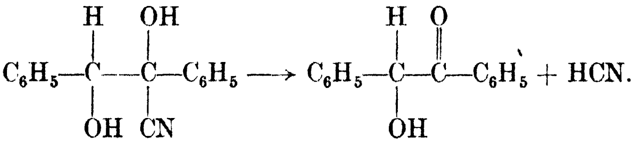
If, as is probable, the energy of the complex is sufficient to enable the second step to take place, the energy of activation for the change will depend upon the nature of the aldehyde (or ester) component, and substituents in this rèagent will influence E, whereas substituents in the second component will not have any marked effect upon E but will change the P factor of the kinetic equation (for the number of complexes which actually give the products will depend upon the reactivity of the second component). Some indication that such is the case is provided in a recent paper by Coombs and Evans,[58] which describes a kinetic study of the reaction of benzaldehyde with acetophenone and the effects of substituents in both reagents.

The Benzoin Reaction (brought about by treatment of benzaldehyde with potassium cyanide) doubtless occurs by the series of changes suggested by Lapworth in 1903.[59] The first product is the cyanohydrin, which then reacts with a second aldehyde molecule as follows:



$$\mathrm{C_6H_5{-}\overset{\displaystyle H \atop |}{\underset{\displaystyle \| \atop O}{C}} + H{-}\overset{\displaystyle OH \atop |}{\underset{\displaystyle | \atop CN}{C}}{-}C_6H_5 \longrightarrow C_6H_5{-}\overset{\displaystyle H \atop |}{\underset{\displaystyle | \atop OH}{C}}{-}\overset{\displaystyle OH \atop |}{\underset{\displaystyle | \atop CN}{C}}{-}C_6H_5.}$$

This is the cyanohydrin of benzoin, and it breaks up, releasing hydrogen cyanide, which goes through the same process again.



$$\mathrm{C_6H_5{-}\overset{\displaystyle H \atop |}{\underset{\displaystyle | \atop OH}{C}}{-}\overset{\displaystyle OH \atop |}{\underset{\displaystyle | \atop CN}{C}}{-}C_6H_5 \longrightarrow C_6H_5{-}\overset{\displaystyle H \atop |}{\underset{\displaystyle | \atop OH}{C}}{-}\overset{\displaystyle O \atop \|}{C}{-}C_6H_5 + HCN.}$$

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[58] *J.C.S.* 1940, 1295. It might be suggested that the catalyst adds to the aldehyde component and also withdraws a proton from the second component. This is not the case, however, since the velocity is proportional to the concentrations of benzaldehyde and acetophenone and to the *first* power of the catalyst concentration.

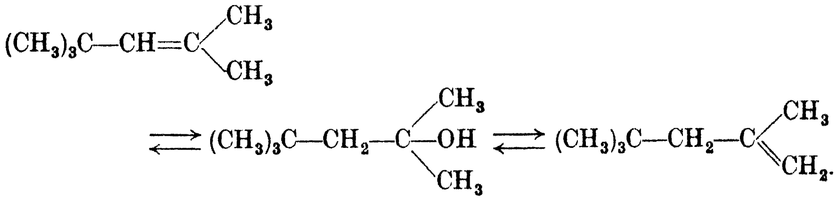
[59] Ibid. 1903, **83**, 1004.

XII

TAUTOMERIC CHANGE

THE meaning now associated with the word 'tautomerism' is stated with admirable clearness in the following definition:[1] 'This term is applied to the property exhibited by certain compounds of behaving in different reactions as if they possessed two or more different constitutions; that is, as if the atoms of the same compound or group were arranged in two or more different ways, expressible by different structural formulae.' An obvious demonstration of tautomeric character is the formation, by a single compound, of *two* sets of isomeric derivatives, as exemplified in nitriles and carbylamines or in Baeyer's two ethyl isatins;[2] in each case only *one* parent substance can be isolated. Again, the hydrolysis of β-bromopropylene and vinyl bromide leads to acetone and acetaldehyde respectively, whereas the products anticipated would be the alcohols $CH_2:C(OH) \cdot CH_3$ and $CH_2:CHOH$ which are isomeric with these carbonyl compounds; this is also an instance of tautomerism.

In 1877 Butlerow[3] interpreted the production of two isomeric *iso*-dibutylenes in the reaction of sulphuric acid with *tert*-butyl alcohol as indicating the equilibrium



$$(CH_3)_3C{-}CH{=}C(CH_3)_2 \rightleftarrows (CH_3)_3C{-}CH_2{-}C(CH_3)_2{-}OH \rightleftarrows (CH_3)_3C{-}CH_2{-}C(CH_3){=}CH_2.$$

He suggested further that all substances which give rise to isomeric derivatives might themselves be equilibrium mixtures of isomerides; in such cases they would exhibit the reactions of both forms and yield derivatives of each. A quite different view was expressed by Laar,[4] to whom we owe the term 'tautomerism'. In all the known examples the parent substances (e.g. HCN and HNC) differed from each other in the position of a hydrogen atom, and Laar suggested that this hydrogen was in a state of continuous oscillation between these positions (similarly to the double bonds in the Kekulé benzene formula). Laar's view was, of course, directly opposed to Butlerow's conception of an equilibrium between isomerides, for the forms giving rise to the different derivatives were regarded as being not isomeric but identical.

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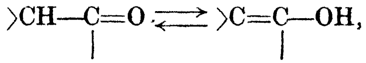
[1] 'Oxford definition.' See Lowry, *Chem. Reviews*, 1927, **4**, 231.

[2] *Ber.* 1883, **16**, 2188.

[3] *Annalen*, 1877, **189**, 44.

[4] *Ber.* 1885, **18**, 648.

Definite evidence in support of Butlerow's theory was obtained in 1896, when the ketonic and enolic forms of certain diketones and ketonic esters were isolated[5] and shown to be easily convertible to the same mixture. The equilibrium in the 'keto-enol' system may be written, in general,



$$>CH-\underset{|}{C}=O \rightleftharpoons >C=\underset{|}{C}-OH,$$

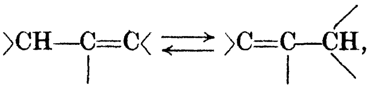
and among the individual isomerides isolated were those of acetyldibenzoylmethane,

$$CH_3\cdot CO\cdot CH(CO\cdot C_6H_5)_2 \rightleftharpoons CH_3\cdot C(OH):C(CO\cdot C_6H_5)_2,$$

and of ethyl formylphenylacetate,

$$CHO\cdot CH(C_6H_5)\cdot COOC_2H_5 \rightleftharpoons CH(OH):C(C_6H_5)\cdot COOC_2H_5.$$

In the same year, too, Hantzsch and Schultze isolated a solid isomeride of phenylnitromethane,[6] which was clearly responsible for the acidic character of the nitro-compound, and which changed spontaneously to the liquid isomeride; the forms are written $C_6H_5\cdot CH_2\cdot NO_2$ and $C_6H_5\cdot CH:NO(OH)$ respectively. Reference should also be made to Fittig's discovery[7] of the interconversion of the ions of $\alpha\beta$- and $\beta\gamma$-unsaturated acids in hot alkaline solution, e.g. $CH_3\cdot CH:CH\cdot COO' \rightleftharpoons CH_2:CH\cdot CH_2\cdot COO'$. This is an example of 'three-carbon tautomerism',



$$>CH-\underset{|}{C}=C< \rightleftharpoons >C=\underset{|}{C}-\overset{/}{\underset{\backslash}{C}}H,$$

similar to that of the *iso*dibutylenes, but differing from the other cases referred to above in that the individual isomerides are both stable substances under ordinary conditions, and are converted to the equilibrium mixture only under the influence of a powerful reagent.

Meanwhile, the problem of the constitution of ethyl acetoacetate, the classic and most widely investigated example of a tautomeric substance, awaited solution. The ester was first prepared in 1863 by Geuther, who assigned to it the enolic formula

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[5] Claisen, *Annalen*, 1896, **291**, 25; Wislicenus, ibid., p. 147; Knorr, ibid. **293**, 70.

[6] *Ber.* 1896, **29**, 699, 2251.

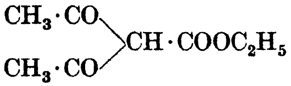
[7] Ibid. 1891, **24**, 82, and later; cf. Linstead, *J.C.S.* 1927, 362.

$$CH_3\cdot C(OH):CH\cdot COOC_2H_5.$$

Frankland, however, preferred the ketonic representation

$$CH_3\cdot CO\cdot CH_2\cdot COOC_2H_5,$$

which was accepted by Wislicenus,[8] whose investigation of the formation and decomposition of the mono- and di-alkyl derivatives of the ester laid the foundation of the extensive uses of the 'acetoacetic ester synthesis'. The metallic derivatives show none of the properties of the organo-metallic compounds, in which a metal is linked to carbon; moreover, the ester can be liberated by addition of acid to these derivatives, which doubtless have an enolic structure, e.g. $CH_3\cdot C(ONa):CH\cdot COOC_2H_5$. They react with alkyl and acyl halides giving products in which the alkyl or acyl group can usually be shown to be linked to *carbon*, i.e. $CH_3\cdot CO\cdot CHR\cdot COOC_2H_5$ and $CH_3\cdot CO\cdot CRR'\cdot COOC_2H_5$, although acetyl chloride, under different conditions, gives both



$$\begin{matrix}CH_3\cdot CO\\CH_3\cdot CO\end{matrix}\Big\rangle CH\cdot COOC_2H_5$$

and $CH_3\cdot C(O\cdot COCH_3):CH\cdot COOC_2H_5$,

ethyl chloroformate produces $CH_3\cdot C(O\cdot COOC_2H_5):CH\cdot COOC_2H_5$, and ammonia and amines yield esters of the type

$$CH_3\cdot C(NR_2):CH\cdot COOC_2H_5.$$

Acetoacetic ester itself gives acetone with dilute acids or alkalis, and *iso*nitrosoacetone, $CH_3\cdot CO\cdot CH:NOH$, with nitrous acid; it also reacts with hydrocyanic acid, sodium bisulphite, hydroxylamine, and phenylhydrazine in accordance with the ketonic formula. On the other hand, it gives a violet coloration with ferric chloride, and is converted to ethyl β-chlorocrotonate, $CH_3\cdot CCl:CH\cdot COOC_2H_5$, by phosphorus pentachloride. It is a typically tautomeric substance in terms of the definition given at the beginning of this chapter.

The rival formulae were, however, the subject of heated controversy until 1911, when Knorr succeeded in isolating the individual isomerides.[9] He crystallized the ketonic form from solutions of the ester in organic solvents at −78°; it gave no immediate colour with ferric chloride (absence of hydroxyl), nor reaction with bromine (absence of C=C). Treatment of the sodium derivative with dry hydrogen chloride at −78° gave the enol, which reacted instantaneously both with ferric chloride and with bromine. Either form gave the equilibrium mixture with the utmost ease, Knorr's successful separation of the isomerides being made possible by the use of a very low temperature at which the speed of interconversion was relatively small. K. H. Meyer later separated the forms by aseptic distillation,[10] consisting in fractionation from a Jena glass or silica vessel previously treated to ensure absence of traces of impurities which catalysed the attainment of equilibrium. Butlerow's original conception of an equilibrium between isomerides was thus finally established in a case where the interconversion is exceedingly easy and rapid.

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[8] *Annalen*, 1877, **186**, 163.

[9] Knorr, Rothe, and Averbeck, *Ber.* 1911, **44**, 1138.

The composition of the equilibrium mixture of ketonic and enolic forms has been investigated by observations of physical properties (e.g. refractivity), but the outstanding method is that devised by K. H. Meyer;[11] it is of a chemical nature, and depends upon the instantaneous reaction of bromine with the enol. Other chemical methods (e.g. the standard processes for determination of —OH) are inapplicable, owing to the rapid transformation of one form to the other. In Meyer's procedure an alcoholic solution of the tautomeric compound is treated with bromine, also in alcohol, and the excess of the halogen immediately removed by addition of a phenol (e.g. β-naphthol or *m*-cresol); the process up to this stage occupies only fifteen seconds, and is carried out at a temperature below 0°. On addition of potassium iodide and acid, the brominated product is reduced in accordance with the equation

$$\text{—CHBr—} + 2\text{HI} = \text{—CH}_2\text{—} + \text{HBr} + \text{I}_2,$$

and the iodine is determined with thiosulphate. The method clearly depends upon the *quantitative* liberation of iodine, which usually occurs with brominated β-diketones and β-ketonic esters (which have the grouping —CO—CH_2—CO— in common). Meyer found that pure acetoacetic ester normally contains 7 per cent. of enol in equilibrium with the ketonic form, and other compounds have much higher proportions, e.g. acetylacetone (80 per cent.) and benzoylacetone (98 per cent.). In solutions the proportions vary widely. Enol is not detectable in ethyl malonate, in spite of its many similarities to acetoacetic ester.

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[10] Meyer and Schoeller, *Ber.* 1920, **53**, 1410.

[11] Ibid. 1911, **44**, 2718; 1912, **45**, 2843. Direct titration with alcoholic bromine is an alternative to the process here described; it is more widely applicable, but probably less accurate.

Although the β-diketones and β-ketonic esters provide the best-known examples of keto-enol tautomerism, another well-established case is that of the α-diketones. The existence of these compounds in the two tautomeric forms has been indicated in a number of investigations,[12] and Dufraisse and Moureu have more recently isolated the pure ketonic and enolic forms of methylbenzylglyoxal, phenylbenzylglyoxal, and phenyl-*p*-methoxybenzylglyoxal.[13] The ketonic forms were obtained by distillation from an alkaline catalyst (sodium carbonate), and the enols by crystallization, also in presence of an alkali or organic base. The isomerides are remarkably stable, and show no tendency to form the equilibrium mixture in the absence of added catalysts.[14] The separation of the tautomeric forms of an α-ketonic ester was achieved by Gault and Weick, who isolated the ketonic and two stereoisomeric enolic isomerides of ethyl phenylpyruvate.[15]

Thus far reference has been made only to cases of mobile hydrogen tautomerism, now usually described by Lowry's term 'prototropy'.[16] Until a relatively recent date, in fact, the term 'tautomerism' was used exclusively to denote the migration of hydrogen.[17] The similar migration of anionic atoms or groups is now recognized, however; this is termed 'anionotropy', and is included under the more general title 'tautomerism'.[18] There is, moreover, no distinction in principle between the tautomerism of crotonic and vinylacetic acids, where interconversion does not proceed at all readily, and that of acetoacetic ester, where it is a matter of great difficulty to isolate either individual form;[19] nor is there any fundamental difference between examples where the equilibrium mixture consists almost entirely of one isomeride and those which normally exist as mixtures of measurable proportions of each. The distinction lies, of course, in the relative stabilities of the tautomeric forms; they may be of the same order of stability, or one may be very much more stable than the other. No attempt is made here to describe the individual characters of the various prototropic systems which have been investigated; twelve such systems are possible by different combinations of the three atoms carbon, nitrogen, and oxygen (e.g. C—C—C, C—N—O, C—C—O, etc.). The object of the present chapter is the consideration of the more general theoretical aspects of tautomeric change, and reference will be made only to the better-known examples, particularly the keto-enol system. For a fuller account of the subject the reader is referred to J. W. Baker's work,[20] in which the individual tautomeric systems are described.

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[12] Widman, *Ber.* 1916, **49**, 484; Jörlander, ibid. 1917, **50**, 406; Malkin and Robinson, *J.C.S.* 1925, **127**, 369.

[13] See Moureu, *Trans. Faraday Soc.* 1928, **24**, 562, and references there cited. Also *Compt. rend.* 1929, **188**, 504.

[14] Compare Lowry, Moureu, and MacConkey, *J.C.S.* 1928, 3167.

[15] *Compt. rend.* 1920, **170**, 1392.

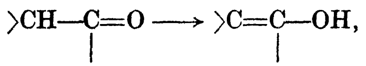
[16] *J.C.S.* 1923, **123**, 828; ref. 1.

[17] As, for example, in K. H. Meyer's famous definition, *Annalen*, 1913, **398**, 49.

[18] No reference is here made to terms such as 'desmotropy', 'merotropy', 'pseudomerism', 'cryptomerism', or 'dynamic isomerism', which have in the past appeared extensively in the literature. They seem now to be quite unnecessary, and indeed confusing.

[19] The most stable specimen of the enol of acetoacetic ester which has been

Evidence of Prototropy in the Halogenation of Carbonyl Compounds. The tautomeric nature of α- and β-diketones and ketonic esters is evident from the foregoing; in a number of cases these compounds have been proved to exist normally as equilibrium mixtures, and the individual ketonic and enolic forms have frequently been isolated. No such clear demonstration is available for monoketones, although any carbonyl compound having at least one hydrogen atom situated in the α-position is *formally* capable of enolization,



$$>\!CH\text{—}\underset{|}{C}\!=\!O \longrightarrow >\!C\!=\!\underset{|}{C}\text{—}OH,$$

and β-bromopropylene, for example, which yields acetone on hydrolysis, is a derivative of the enol. Further, an enolic constitution was ascribed by Freer[21] to certain metallic derivatives of acetone, and the presence of enol in alkaline solutions has been inferred from the nature of the oxidation products.[22] But the main evidence that monoketones can undergo prototropic change has been derived from a study of the kinetics of their reactions with halogens.

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prepared had a half-life period of 500 hours (Rice and Sullivan, *J. Amer. Chem. Soc.* 1928, **50**, 3048).

[20] Baker, *Tautomerism* (Routledge & Sons, 1934). This work contains, *inter alia*, an account of the investigations of the three-carbon system carried out by Kon, Linstead, and their collaborators at Imperial College, London.

[21] *Amer. Chem. J.* 1891, **13**, 322, and later; cf. Evans and Nicoll, *J. Amer. Chem. Soc.* 1925, **47**, 2789.

[22] Witzemann, ibid. 1917, **39**, 2657; cf. Denis, *Amer. Chem. J.* 1907, **38**, 561.

It was first suggested by Lapworth[23] that the characteristic replacement of the α-hydrogen atom of a carbonyl compound might involve a preliminary change to enol. The suggestion was based upon his discovery that bromine reacts with acetone in dilute aqueous solution at a rate which is proportional to the concentration of the ketone but independent of that of the halogen. It was clear that the reaction must occur in at least two stages, that in which the halogen is involved being too rapid for measurement. The further observation that the velocity of bromination was increased very greatly by the introduction of mineral acid led Lapworth to suggest that a relatively slow change to the enolic form (catalysed by acids) is followed by very rapid reaction of the latter with bromine:

$$CH_3\cdot CO\cdot CH_3 \xrightarrow{\text{(slow)}} CH_2{:}C(OH)\cdot CH_3 \xrightarrow{Br_2\text{(rapid)}} CH_2Br\cdot CO\cdot CH_3+HBr.$$

On Lapworth's view, therefore, the velocity actually measured is that of the prototropic change; a convenient method of determining the speeds of such changes is thus provided.[24] Subsequent investigations, by Dawson and his collaborators,[25] of the iodination of various ketones and of acetaldehyde, confirmed the view that these compounds react with halogens in their enolic forms. A similar demonstration has since been given for typical α- and γ-ketonic acids (pyruvic and laevulinic),[26] and the conclusion may be drawn that, with certain reservations indicated below, compounds containing a carbonyl group with at least one hydrogen atom situated in the α-position with respect to this group react with halogens in their enolic forms.

It is important to realize that it is the ketonic carbonyl group and not that of carboxyl or carbethoxyl which is concerned in the prototropy of ketonic acids and their esters, and, in view of the absence, in carboxylic acids such as acetic and its homologues, of the properties which are characteristic of ketones, it is unsafe to force an analogy between the two types of compounds. Nevertheless, the α-bromination of saturated aliphatic acids appears to bear some resemblance to that of typical carbonyl compounds. At a somewhat elevated temperature one α-hydrogen is replaced, and if no α-hydrogen is present halogenation does not occur, as, for example, in the case of trimethylacetic acid.[27] Moreover, the reaction is catalysed by hydrogen chloride and hydrogen bromide, and Lapworth suggested tentatively that here also enolization might precede halogenation. This view received much support.[28] Subsequent investigations,[29] however, have shown that in the bromination of acetic acid and its homologues (*a*) the velocity is dependent upon the concentration of the halogen,[30] (*b*) the catalytic effect of halogen acids is specific, and not common to acids in general, and (*c*) a small quantity of the acid bromide accelerates the bromination enormously, the velocity now being proportional to the concentrations of both acid bromide and bromine. It has long been known that the bromides of carboxylic acids react with halogens more rapidly than do the acids themselves, the well-known Hell-Volhard method of bromination being based upon this fact, and the observations noted above are in harmony with the following scheme for the bromination of the acids. The bromine first reacts with the acid bromide, the brominated *acid* then being formed as the result of a reaction between the unsubstituted acid and the brominated bromide,[31]

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[23] *J.C.S.* 1904, **85**, 30.

[24] When both tautomeric forms are stable substances, as in the case of crotonic and vinylacetic acids, the catalysed transformation of the one into the other may be followed by analytical methods. This procedure is not applicable to systems where one form is of such low relative stability that its concentration is at no time sufficiently high for measurement (e.g. the enolic form of acetone). The velocity of prototropic change may now be found by Lapworth's halogenation method referred to above. Other methods employ the rate of loss of optical activity in cases where the atom from which the mobile proton migrates is a centre of asymmetry (Conant and Carlson, *J. Amer. Chem. Soc.* 1932, **54**, 4048), or the rate of exchange of hydrogen for deuterium (Wilson, *Trans. Faraday Soc.* 1938, **34**, 175 and refs. there cited).

[25] *J.C.S.* 1909, **95**, 1860; 1910, **97**, 2048; 1911, **99**, 1740; 1912, **101**, 1503; 1914, **105**, 1275.

[26] Hughes and Watson, ibid. 1929, 1945.

$$R\cdot CH_2\cdot COBr + Br_2 = R\cdot CHBr\cdot COBr + HBr,$$

$$R\cdot CHBr\cdot COBr + R\cdot CH_2\cdot COOH \rightleftarrows R\cdot CH_2\cdot COBr + R\cdot CHBr\cdot COOH.$$

The acid bromide is then free to go through the same series of reactions again. This scheme brings into harmony all recorded observations of the catalysed bromination of carboxylic acids, the actual role of all accelerators (such as phosphorus, acetic anhydride, or halogen acid) being the production of a small quantity of the acid bromide. Chlorination follows a similar course.[32]

In spite, however, of the absence of any tendency on the part of the saturated monocarboxylic acids to undergo prototropic change, malonic acid reacts with halogens in its enolic form, the velocity being, as in the case of acetone, independent of the concentration of the halogen.[33] Moreover, Meyer has demonstrated the presence of enol in the product when an alcoholic solution of ethyl sodiomalonate is acidified, although the ester itself normally contains no detectable quantity of this isomeride. There are also indications that succinic acid may be brominated through its enolic form, the reaction being catalysed by mineral acids.[34]

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[27] Reformatzsky, *Ber.* 1890, **23**, 1594.

[28] e.g. Aschan, ibid. 1912, **45**, 1913; 1913, **46**, 2162; Ward, *J.C.S.* 1922, **121**, 1161; 1923, **123**, 2207.

[29] Watson, *J.C.S.* 1925, **127**, 2067; *Chem. Reviews*, 1930, **7**, 173.

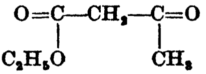
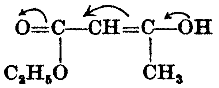
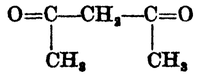
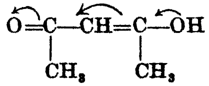
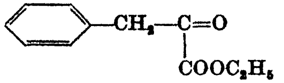
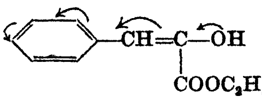
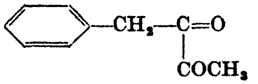
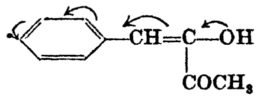
[30] Compare Hell and Urech, *Ber.* 1880, **13**, 531.

[31] For further evidence in support of this mechanism see ref. 29. The second reaction actually occurs in two stages, involving the production of a mixed anhydride as intermediate (Watson and Gregory, *J.C.S.* 1929, 1373). When no catalyst is added the change may commence by the reaction of bromine with a trace of moisture present.

[32] Watson and Roberts, *J.C.S.* 1928, 2779.

The available data indicate, therefore, all grades of stability of the enol, extending from those instances where it is isolatable and present normally in equilibrium with the ketonic form in measurable, and sometimes major quantity, to cases where its stability is so small that it cannot even function as an intermediate in halogenation and other processes. An interpretation of these vast differences in stability may be found in the light of the conception of mesomerism, which has been outlined in Chapter I.

In all enols which are known to have considerable stability, the system is terminated by one of the groups C=O, C≡N, or C_6H_5, and this group is separated from hydroxyl by a chain of alternate double and single linkages.[35] They are actually mesomeric structures, therefore, in which the electrons are displaced as indicated by the curved arrows in the formulae of the table which follows:

Compound	*Ketonic form*	*Enolic form*
Acetoacetic ester	 $O{=}\underset{C_2H_5O}{C}{-}CH_2{-}\underset{CH_3}{C}{=}O$	 $O{=}\underset{C_2H_5O}{C}{-}CH{=}\underset{CH_3}{C}{-}OH$
Acetylacetone	 $O{=}\underset{CH_3}{C}{-}CH_2{-}\underset{CH_3}{C}{=}O$	 $O{=}\underset{CH_3}{C}{-}CH{=}\underset{CH_3}{C}{-}OH$
Ethyl phenylpyruvate		
Methylbenzylglyoxal		

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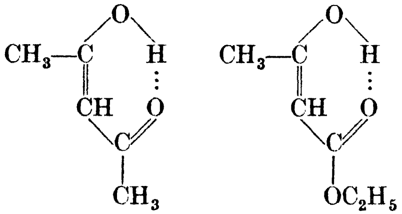
[33] Meyer. *Ber.* 1912, **45,** 2864; West, *J.C.S.* 1924, **125,** 1277. The latter author suggests that in the bromination of monobromomalonic acid *rapid* enolization is followed by a *measurable* reaction with bromine, the change being bimolecular.

[34] Hughes and Watson, *J.C.S.* 1930, 1733.

[35] Compare Watson and Yates, ibid. 1933, 221.

All these enols must therefore have considerable resonance energies, which will lead to an increase in stability. It has further been pointed out by Sidgwick,[36] with regard to acetylacetone and acetoacetic ester, that the greater solubility of the enols in non-aqueous solvents, and their greater volatility as compared with the ketonic isomerides, indicates the formation of a hydrogen bond between the hydroxyl and the carbonyl groups as in the formulae



A free hydroxyl group would be expected to lead to a *smaller* solubility in non-hydroxylic solvents, and also to association, with a consequent *decrease* in volatility. Such formation of a hydrogen bond will result in a further increase of resonance energy and therefore of stability.[37]

In the saturated monocarboxylic acids, on the other hand, transformation to enol, $-\mathrm{C}\begin{smallmatrix}\diagup\mathrm{O}\\ \diagdown\mathrm{O}\end{smallmatrix}\Big\}\,\mathrm{H} \longrightarrow =\mathrm{C}\begin{smallmatrix}\diagup\mathrm{OH}\\ \diagdown\mathrm{OH}\end{smallmatrix}$, would destroy the carboxyl group, with a *loss* of the resonance energy associated with it, and a consequent loss of stability. It is not surprising, therefore, that they are never found to undergo prototropic change. Dicarboxylic acids, such as malonic and succinic, however, can change to enol while retaining the resonance energy due to *one* carboxyl group, e.g. $\mathrm{COOH{-}CH_2{-}COOH} \longrightarrow \mathrm{COOH{-}CH{=}C}\begin{smallmatrix}\diagup\mathrm{OH}\\ \diagdown\mathrm{OH}\end{smallmatrix}$. The halides of the monocarboxylic acids, such as acetyl chloride and bromide, also show no indication of prototropy, and they are brominated at a rate which is proportional to the concentration of halogen.[38] Direct reaction of the halogen with the ketonic form is therefore probable, and must be due to the influence of halogen attached directly to carbonyl. No clear interpretation of this case has been given, however.

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[36] *J.C.S.* 1925, **127**, 907; cf. Lowry and Burgess, ibid. 1923, **123**, 2114.

[37] See Chap. I. Other instances of intramolecular hydrogen bond formation are dealt with in Chap. XV.

[38] Watson, *J.C.S.* 1928, 1137.

Acid and Base Catalysis. An important feature of the majority of prototropic changes is the catalytic influence of *both* acids and bases; this is observed also in certain other reactions, such as the hydrolysis of esters[39] and some addition processes.[40] Ostwald and Arrhenius attributed such catalysis exclusively to hydrogen and hydroxyl ions, a view which was based upon the observation by the former (1884–7) that there was an approximate proportionality between the catalytic influence of an acid or base and its electrical conductivity. The relationship was demonstrated for thirty-four acids by measurements of the velocity of hydrolysis of methyl acetate or the inversion of cane sugar, and for four alkalis and thirteen nitrogenous bases by a study of their catalytic effects upon the hydrolysis of ethyl acetate. In spite of the approximate nature of this relationship, and of the absence of any interpretation of the observed effects of neutral salts, the Ostwald-Arrhenius conception was not seriously challenged for twenty years. From 1907 onwards, however, a whole series of observations have shown that a much broader view must be taken, and the catalytic effects of a variety of molecules and ions are now recognized.

The first step was the inclusion of undissociated molecules of acids as catalysts,[41] but this so-called 'dual theory' of catalysis (a term introduced by Dawson) was very soon extended. The work of Brönsted upon the decomposition of nitroamide,[42] and of Dawson upon the iodination of acetone,[43] made it necessary to ascribe catalytic influences to the anions of weak acids (of which hydroxyl is clearly a special example). Finally, a definite, though relatively small catalytic action of water molecules has been observed in at least two reactions,[44] and the velocity of an acid-base catalysed change in an aqueous medium is therefore represented

$$v = v_{\mathrm{H}}+v_{\mathrm{OH}}+v_{\mathrm{M}}+v_{\mathrm{A}}+v_{\mathrm{H_2O}}$$

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[39] Chap. IX.

[40] Chap. XI.

[41] Acree and Johnson, *Amer. Chem. J.* 1907, **37**, 410; **38**, 258; Lapworth. *J.C.S.* 1908, **93**, 2197; Goldschmidt and Thuesen, *Z. physikal. Chem.* 1910, **70**, 627; 1912, **81**, 30; Bredig, Miller, and Braune, *Z. Elektrochem.* 1912, **18**, 535; Snethlage, ibid., p. 539; Dawson and Powis, *J.C.S.* 1913, **103**, 2135; Dawson and Reiman, ibid. 1915, **107**, 1426.

[42] Brönsted and Pedersen, *Z. physikal. Chem.* 1924, **108**, 185; Brönsted and Duus, ibid. 1925, **117**, 299.

[43] Dawson and Carter, *J.C.S.* 1926, 2282.

[44] Brönsted and Guggenheim, *J. Amer. Chem. Soc.* 1927, **49**, 2554; Dawson and Kay, *J.C.S.* 1928, 543. Compare Hudson, *J. Amer. Chem. Soc.* 1907, **29**, 1571.

(where the suffixes indicate catalysis by hydrogen ion, hydroxyl ion, undissociated acid, anion of weak acid, and water respectively).

These catalysts are divisible into two classes, viz. those which can release a proton (e.g. $H_3O^{\oplus}$, undissociated acid), and those which can unite with a proton (e.g. hydroxyl ion, anion of weak acid, organic bases). Water has both properties ($H_3O^{\oplus} \leftarrow H_2O \rightarrow OH^{\ominus}$). In accordance with a suggestion made independently by Lowry[45] and by Brönsted[46] in 1923, the terms 'acid' and 'base' are now endowed with a wider significance, and include all these substances. According to this generalized conception, an 'acid' is a proton donator and a 'base' is a proton acceptor. Brönsted expresses the relationship between 'acids' and 'bases' as

$$\text{Acid} \rightleftarrows \text{Base} + H^{\oplus};$$

the 'acid' can release a proton to give the 'conjugate base', and, conversely, a 'base' can combine with a proton forming the 'conjugate acid'. It is interesting to note that, in the light of this conception, ammonia is a base while ammonium ion is an acid, $NH_4^{\oplus} \leftrightarrows NH_3 + H^{\oplus}$. The modern theory of acid and base catalysis thus substitutes, for the 'hydrogen ion' and 'hydroxyl ion' of the Ostwald-Arrhenius conception, the terms 'acid' and 'base' defined in the generalized manner.

It is evident that, if a reaction is catalysed both by acids and by bases, its velocity must have a minimum value for a certain composition of the catalysing medium, and as early as 1893 such a minimum was observed in the velocity of hydrolysis of methyl acetate.[47] A similar 'minimum point' has more recently been observed in the iodination of acetone, the mutarotation of glucose, and the hydrolysis of various esters.[48] The conditions existing at the minimum point have been calculated by Dawson and Dean in the following way.[49] They consider an acid-base catalysed reaction proceeding in aqueous solution in presence of a constant concentration c of a weak acid HA (e.g. acetic acid), and a variable concentration of its salt. Unless the amount of salt is very great, catalysis by hydroxyl may be neglected, as may also the very small catalytic effect of the water molecules. The velocity equation thus becomes

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[45] *Chem. and Ind.* 1923, **42**, 43.

[46] *Rec. trav. chim.* 1923, **42**, 718. Compare *J. Phys. Chem.* 1926, **30**, 777; *Chem. Reviews*, 1928, **5**, 231; *Trans. Faraday Soc.* 1928, **24**, 630.

[47] Wijs, *Z. physikal. Chem.* 1893, **11**, 492.

[48] Dawson and Carter, ref. 43; Dawson and Lowson, *J.C.S.* 1927, 2444; Groocock, Ingold, and Jackson, *J.C.S.* 1930, 1039; Lowry and Smith, ibid. 1927, 2539; Euler *et al.*, *Z. anorg. Chem.* 1925, **146**, 45; 1926, **152**, 113.

[49] *J.C.S.* 1926, 2872; cf. Dawson, *Trans. Faraday Soc.* 1928, **24**, 640.

$$v = v_{\mathrm{H}}+v_{\mathrm{A}}+v_{\mathrm{M}} = k_{\mathrm{H}}[\mathrm{H}^{\cdot}]+k_{\mathrm{A}}[\mathrm{A}']+k_{\mathrm{M}}[\mathrm{HA}]. \tag{1}$$

Assuming the Ostwald Dilution Law,

$$[\mathrm{H}^{\cdot}][\mathrm{A}'] = \mathrm{K}(c-[\mathrm{H}^{\cdot}]),$$

whence
$$v = k_{\mathrm{H}}[\mathrm{H}^{\cdot}]+\frac{k_{\mathrm{A}}\mathrm{K}(c-[\mathrm{H}^{\cdot}])}{[\mathrm{H}^{\cdot}]}+k_{\mathrm{M}}(c-[\mathrm{H}^{\cdot}])$$

$$= (k_{\mathrm{H}}-k_{\mathrm{M}})[\mathrm{H}^{\cdot}]+\frac{k_{\mathrm{A}}\mathrm{K}c}{[\mathrm{H}^{\cdot}]}+k_{\mathrm{M}}c-k_{\mathrm{A}}\mathrm{K}, \tag{2}$$

the last term being negligible.

At the minimum point $dv/d[\mathrm{H}^{\cdot}] = 0$, and hence the concentration of hydrogen ion at this point becomes

$$[\mathrm{H}^{\cdot}]_i = \sqrt{\left(\frac{k_{\mathrm{A}}\mathrm{K}c}{k_{\mathrm{H}}-k_{\mathrm{M}}}\right)}. \tag{3}$$

Substituting in (2), the velocity at the minimum point is

$$v_i = 2\sqrt{\{(k_{\mathrm{H}}-k_{\mathrm{M}})k_{\mathrm{A}}\mathrm{K}c\}}+k_{\mathrm{M}}c. \tag{4}$$

From (2) and (4) it is evident that

$$(v_{\mathrm{H}})_i = (v_{\mathrm{A}})_i = \sqrt{\{(k_{\mathrm{H}}-k_{\mathrm{M}})k_{\mathrm{A}}\mathrm{K}c\}},$$

and the minimum point is thus characterized by the equality of the effects of the hydrogen ions and the anions.

Considering, now, two *equal* velocities, one on each side of the minimum ('isocatalytic') point, where the concentrations of hydrogen ions are $[\mathrm{H}^{\cdot}]_1$ and $[\mathrm{H}^{\cdot}]_2$ respectively, equation (2) leads to the relationship

$$(k_{\mathrm{H}}-k_{\mathrm{M}})[\mathrm{H}^{\cdot}]_1+\frac{k_{\mathrm{A}}\mathrm{K}c}{[\mathrm{H}^{\cdot}]_1} = (k_{\mathrm{H}}-k_{\mathrm{M}})[\mathrm{H}^{\cdot}]_2+\frac{k_{\mathrm{A}}\mathrm{K}c}{[\mathrm{H}^{\cdot}]_2}$$

which, on dividing throughout by $(k_{\mathrm{H}}-k_{\mathrm{M}})$ and rearranging, becomes

$$[\mathrm{H}^{\cdot}]_1[\mathrm{H}^{\cdot}]_2 = \frac{k_{\mathrm{A}}\mathrm{K}c}{k_{\mathrm{H}}-k_{\mathrm{M}}} = [\mathrm{H}^{\cdot}]_i^2$$

or
$$(\mathrm{pH})_1+(\mathrm{pH})_2 = 2(\mathrm{pH})_i.$$

The plot of velocity against pH[50] is therefore a symmetrical curve. It is actually a catenary, as shown in Fig. 17, which is reproduced from Dawson and Dean's paper; the total velocity is represented by the unbroken curve, and the dotted lines represent the partial velocities due to catalysis by hydrogen ion, anion, and undissociated acid respectively. Excellent agreement between theory and experiment has been obtained by Dawson and his collaborators, both for the acetone-iodine reaction and for ester hydrolysis.[48,49] For each value of *c*, the constant concentration of acid, there is a separate catenary, and the reaction velocities for *all* possible mixtures of a weak acid and its salt are represented by a series of curves which

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[50] pH is the hydrogen ion exponent, representing $-\log[\mathrm{H}^{\cdot}]$.

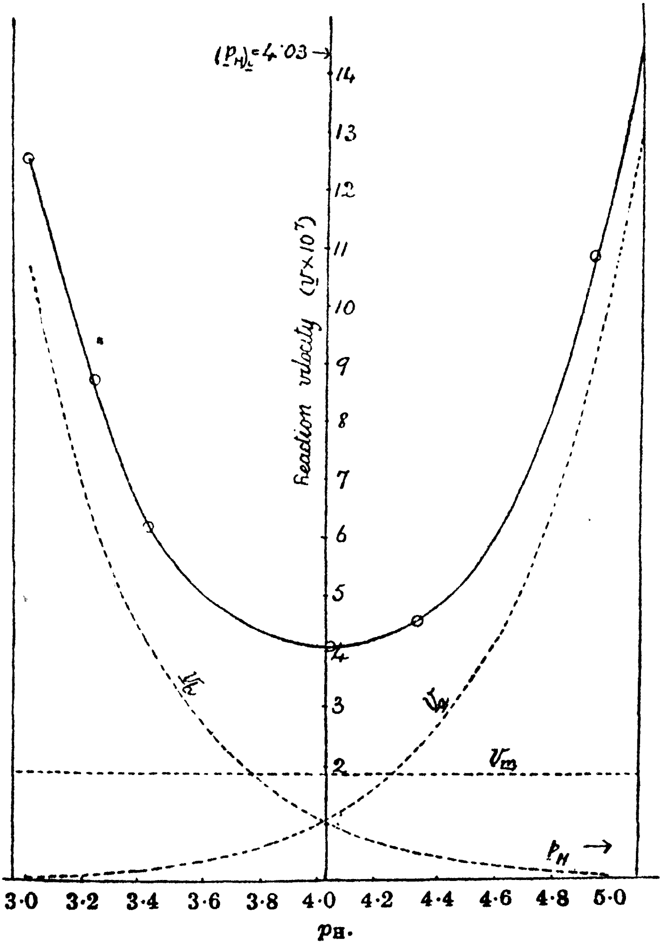


FIG. 17. The catalytic catenary for the acetone-iodine reaction in presence of acetic acid and varying concentrations of sodium acetate. (Reproduced from Dawson and Dean, *J.C.S.* 1926, 2875.)

form a catenary surface, the coordinates of which are expressed in terms of the velocity, the hydrogen ion concentration, and the acid concentration.[51] Dawson and Key have shown that the conclusions reached are not invalidated by the influence of the ionic strength of the medium upon the reaction velocity.[52] Neutral salt effects were observed by Arrhenius, and are accounted for by Brönsted's theory of reaction velocity in solution.[53] Dawson and Key's results for sodium chloride solutions up to 4 M in concentration are closely similar, however, to those obtained in the absence of the catalytically inert salt.

An investigation of the bromination of a series of halogenated acetones in 50 per cent. and 75 per cent. acetic acid medium has revealed a very notable influence of substituents upon the isocatalytic point.[54] As the number of halogen atoms is increased (e.g. from acetone to tetrabromoacetone), this point occurs at continuously higher acid concentration. Thus, in the case of acetone, the medium itself is on the acid side of the isocatalytic point, and introduction of mineral acid leads to a continuous increase of velocity. For monobromo-, *as*-dibromo-, and *s*-dibromo-acetones, however, addition of acid at first causes a *decreased*, and later an increased speed; the point of minimum velocity is reached, in the three cases, by introduction of hydrochloric acid at concentrations of 0·002 M, 0·2 M, and 0·45 M respectively. The influence of acid upon the bromination of $\alpha\alpha\alpha$-tribromo- and *as*-tetrabromo-acetones is very striking; the speed is *decreased* by acid up to 2 M concentration, and the isocatalytic point must therefore occur at a higher acidity even than this. This movement of the minimum point into regions of higher acidity clearly indicates a decrease in the effectiveness of acid catalysts as compared with basic catalysts, i.e. a decrease in the ratio k_H/k_A. It is brought about by the presence of *electron-attractive* substituents (halogens) in the molecule, and is to be expected since such a substituent will facilitate attack by a base (nucleophilic reagent) and operate against the attack by an acid (electrophilic reagent).[55]

[51] Dawson, *J.C.S.* 1927, 213, 756.

[52] Ibid. 1928, 1248.

[53] *Z. physikal. Chem.* 1922, **102**, 169; 1925, **115**, 337; cf. ref. 46.

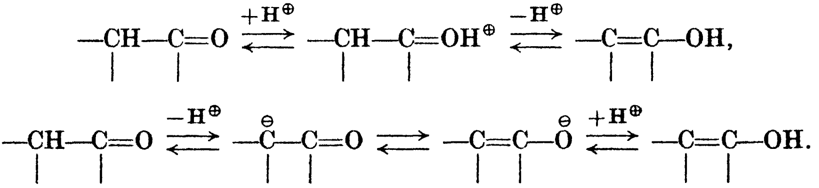
[54] Watson and Yates, *J.C.S.* 1932, 1207.

[55] The susceptibility of the higher halogenated acetones to base-catalysed prototropy is to be correlated with the stability of their hydrates and other addition compounds and with the fact that they undergo haloform cleavage (Edwards, Evans, and Watson, *J.C.S.* 1937, 1942).

Mechanism of Prototropic Change. As early as 1890 the suggestion was made that tautomeric change is preceded by the ionization of the mobile hydrogen,[56] and some confirmation was found in the discovery that the interconversion of tautomerides was facilitated by solvents of good ionizing power.[57] The development of this view has been admirably summarized by the late Sir J. F. Thorpe in his Presidential Address to the Chemical Society, 1931,[58] and he concludes with the following criticism:

> 'the large differences between organic and inorganic chemistry and the fact that the former is so largely the "chemistry of the covalencies" must always introduce an element of reserve into the reception of any theory postulating complete ionic reaction in virtually non-conducting media. Such considerations undoubtedly influenced the earlier supporters of the dissociation hypothesis and led them to qualify their views by such expressions as "a weak kind of dissociation", "a species of dissociation", "a phase of disorganization", and so on.'

Whatever be the exact mechanisms involved, it is obvious that a prototropic change which is catalysed both by acids and by bases must proceed by *two* distinct routes. This was pointed out in 1902 by Lapworth and Hann,[59] who suggested two series of changes which, in their essentials, have usually been accepted. Taking the prototropy of a carbonyl compound as an example, these 'acid' and 'basic' mechanisms may be written as follows:



$$-\underset{|}{\mathrm{CH}}-\underset{|}{\mathrm{C}}=\mathrm{O} \xrightleftharpoons{+\mathrm{H}^{\oplus}} -\underset{|}{\mathrm{CH}}-\underset{|}{\mathrm{C}}=\mathrm{OH}^{\oplus} \xrightleftharpoons{-\mathrm{H}^{\oplus}} -\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}-\mathrm{OH},$$

$$-\underset{|}{\mathrm{CH}}-\underset{|}{\mathrm{C}}=\mathrm{O} \xrightleftharpoons{-\mathrm{H}^{\oplus}} -\underset{|}{\overset{\ominus}{\mathrm{C}}}-\underset{|}{\mathrm{C}}=\mathrm{O} \rightleftharpoons -\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}-\overset{\ominus}{\mathrm{O}} \xrightleftharpoons{+\mathrm{H}^{\oplus}} -\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}-\mathrm{OH}.$$

The initial step is thus either addition of proton at carbonyl oxygen (acid catalysis), or removal of α-hydrogen as proton (basic catalysis). The 'basic mechanism' is actually a restatement of the earlier 'ionization theory' of tautomeric change, and in more recent years the series of transformations

ionization—rearrangement of ion—addition of proton

has been postulated by Ingold, Shoppee, and Thorpe for three-carbon tautomerism,[60] and by Lowry for the keto-enol change.[61] In the former case the interconversion is observed only when the system is activated by a group, such as CO, $COOC_2H_5$, or CN, which causes electron-recession by electromeric displacements, e.g.

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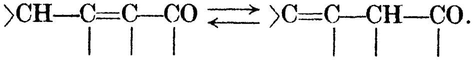
[56] Goldschmidt, *Ber.* 1890, **23**, 257.

[57] e.g. Claisen, *Annalen*, 1896, **291**, 86; Brühl, *Ber.* 1899, **32**, 2326.

[58] *J.C.S.* 1931, 1015.

[59] Ibid. 1902, **81**, 1512.



$$>\!CH-\underset{|}{C}=\underset{|}{C}-\underset{|}{C}O \rightleftarrows >\!C=\underset{|}{C}-\underset{|}{C}H-\underset{|}{C}O.$$

The most powerful catalysts are those of the basic type, but acid catalysis has been observed,[62] and it may be concluded that the C=O or C≡N group provides the point of attack for the acid catalyst.

In a comprehensive discussion of base-catalysed prototropy, Pedersen has pointed out[63] that the ionization theory implies that there is no difference in principle between the acidic characters of a *pseudo*-acid (e.g. ketone, nitro-compound) and of a true acid (e.g. enol, *iso*-nitro-compound) since both are genuine acids, although the former is much weaker than the latter. On modern views, the ions $>\!\overset{\ominus}{C}-\underset{|}{C}=O$ and $>\!C=\underset{|}{C}-\overset{\ominus}{O}$ are not separate entities, but the unperturbed structures of a mesomeric anion $>\!\overbrace{C-\underset{|}{C}-O}^{\ominus}$, and the series of changes becomes

ketone → mesomeric anion → enol.

There is actually no need, however, to postulate the actual formation of the enol itself as an intermediate in a reaction such as bromination, for it is quite probable that it is this ion which reacts rapidly with the halogen; on the basis of the above mechanism for base-catalysed bromination, the speed actually measured would be that of ionization, i.e. the speed of removal of the proton by the base.[64]

While the first step in these mechanisms of prototropy is either the addition or the removal of a proton, each scheme is completed by the opposite change, i.e. the removal (in acid catalysis) or addition (in basic catalysis) of a proton. This is in harmony with Lowry's view that prototropic changes can proceed only in the presence of both a proton donator (acid) and a proton acceptor (base).[65] As early as 1899 experiments on the prototropy of nitrocamphor,

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[60] *J.C.S.* 1926, 1477.

[61] Ibid. 1927, 2557; cf. Hsu and Wilson, ibid. 1936, 623.

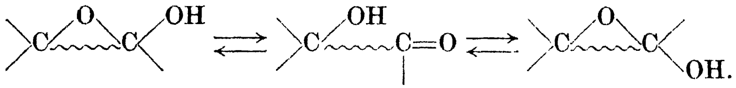
[62] Kon, ibid. 1931, 248; 1934, 623.

[63] *J. Physical Chem.* 1933, **37**, 751; 1934, **38**, 581, 601; *Trans. Faraday Soc.* 1938, **34**, 237.

[64] Wilson, ibid. 1938, **34**, 175.

$$\rangle \mathrm{CH{-}NO{=}O} \rightleftharpoons \rangle \mathrm{C{=}NO{-}OH},$$

which can be followed polarimetrically, had shown that the mutarotation, usually complete in three days, is sometimes arrested in a pure anhydrous solvent for long and variable periods of time extending up to two or three weeks.[66] At a later date similar observations were made during a study of the mutarotation of tetramethylglucose,[67] which probably involves two prototropic changes,



For example, one experiment in chloroform medium showed no change after ten days. It was finally demonstrated that, while neither pyridine (proton acceptor) nor cresol (proton donator) individually catalysed the mutarotation, the two in conjunction formed a powerful catalyst.[68] Lowry therefore concluded that prototropic changes require the presence of a reagent to provide a proton, and also of one to remove a proton, and he defined the period of induction observed in mutarotation as a 'period of time during which a pure material is taking up the impurities that are needed to promote the change'. Similar arrests of variable duration have been observed in the bromination of acetone and of ketonic acids in anhydrous solvents; there is a period of induction which may vary from ten minutes to several hours.[26]

The series of changes first suggested by Lapworth and Hann to represent acid- and base-catalysed prototropy have thus met with general acceptance, and it is a tribute to the insight displayed by these authors that more than thirty years of intensive research have led to no results which are contrary to their postulated mechanisms. A slightly modified scheme has been put forward recently.[69] The attack of the catalyst is visualized in the manner already described .

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[65] *J.C.S.* 1925, 1371. At an earlier date (ref. 45) Lowry had correlated the observed arrests in the mutarotation of nitrocamphor with the lack of acidity of pure liquids and the universal solvation of the hydrogen ion in solution, all of which he ascribed to the 'extreme reluctance of a hydrogen nucleus to lead an isolated existence'.

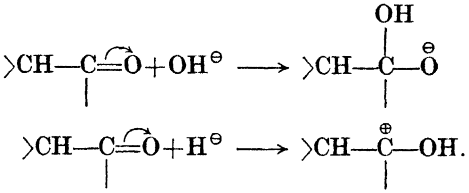
[66] Lowry, *J.C.S.* 1899, **75**, 211.

[67] Lowry and Richards, ibid. 1925, **127**, 1385.

[68] Lowry and Faulkener, ibid., p. 2883.

[69] Watson, Nathan, and Laurie, *J. Chem. Physics*, 1935, **3**, 170.

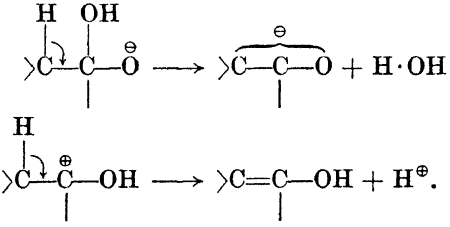
in connexion with the addition of nucleophilic reagents at double bonds;[70] co-ordination of the catalyst at carbonyl carbon (for base catalysis) or oxygen (for acid catalysis) leads to the activation of the carbonyl group:



$$>\mathrm{CH}{-}\underset{|}{\mathrm{C}}{=}\mathrm{O}+\mathrm{OH}^{\ominus} \longrightarrow >\mathrm{CH}{-}\underset{|}{\overset{\mathrm{OH}}{\mathrm{C}}}{-}\overset{\ominus}{\mathrm{O}}$$

$$>\mathrm{CH}{-}\underset{|}{\mathrm{C}}{=}\mathrm{O}+\mathrm{H}^{\ominus} \longrightarrow >\mathrm{CH}{-}\underset{|}{\overset{\oplus}{\mathrm{C}}}{-}\mathrm{OH}.$$

The essential difference between this representation and the schemes of Lapworth and Hann is that the first step in the basic mechanism is the addition of the catalyst at carbonyl carbon, instead of the removal of the α-proton. The primary process is analogous to cyanohydrin formation or alkaline hydrolysis of an ester, rather than to ionization in the more powerfully acidic systems. The energized complex thus formed, either in the base-catalysed or the acid-catalysed change, may then undergo either of two transformations: it may fall apart re-forming the original reagents (reverse of the changes represented above), or it may lose an α-proton to give the mesomeric ion or the enol:



$$>\overset{\mathrm{H}}{\mathrm{C}}{-}\underset{|}{\overset{\mathrm{OH}}{\mathrm{C}}}{-}\overset{\ominus}{\mathrm{O}} \longrightarrow >\mathrm{C}{-}\underset{|}{\mathrm{C}}{-}\mathrm{O}^{\ominus}+\mathrm{H{\cdot}OH}$$

$$>\overset{\mathrm{H}}{\mathrm{C}}{-}\underset{|}{\overset{\oplus}{\mathrm{C}}}{-}\mathrm{OH} \longrightarrow >\mathrm{C}{=}\underset{|}{\mathrm{C}}{-}\mathrm{OH}+\mathrm{H}^{\oplus}.$$

On this view, the velocity of the prototropic change will depend upon two factors, viz. the rate of reaction of ketone and catalyst and the proportion of the energized complex which is transformed to mesomeric anion or to enol. A similar mechanism is applicable to other types of prototropy, in addition to the keto-enol system. The known facts are interpreted equally well by this scheme or by that of Lapworth and Hann; the new mechanism is attractive in that it brings into line a large number of reactions of the carbonyl group.

Anionotropy. Tautomeric changes involving the migration of an anion have not been subjected to such extensive investigation as have prototropic changes. Nevertheless, the general rules governing anionotropy have been laid down by Burton and Ingold[71] as the result of their study of the interconversion of esters of α-phenylallyl alcohol, $C_6H_5\cdot CH(OH)\cdot CH : CH_2$, and cinnamyl alcohol, $C_6H_5\cdot CH : CH\cdot CH_2OH$. The *p*-nitrobenzoate of the former was found to pass smoothly into that of the latter in boiling acetic anhydride medium,

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[70] Preceding chapter, p. 157.

$$C_6H_5\cdot CHX\cdot CH{:}CH_2 \longrightarrow C_6H_5\cdot CH{:}CH\cdot CH_2X$$

$$(X = p\text{-}NO_2\cdot C_6H_4\cdot COO).$$

In presence of tetramethylammonium acetate, however, the product was a mixture of cinnamyl acetate and cinnamyl *p*-nitrobenzoate; this observation was taken to indicate that complete removal of the anion X had occurred, giving a mesomeric organic cation, and the stages of the anionotropic change were therefore represented as follows:

$$R\cdot CHX\cdot CH{:}CH_2 \longrightarrow X^{\ominus} + R\cdot \overset{\oplus}{\overparen{CH\cdot CH\cdot CH_2}} \longrightarrow R\cdot CH{:}CH\cdot CH_2X.$$

In accordance with this mechanism, the ease with which the conversion occurs was found to be governed by three factors:

(*a*) The ability of X to form a stable anion, as indicated by the strength of the acid HX. Thus the alcohols ($X = OH$) were not interconvertible, whereas acetic anhydride (producing the corresponding acetates, $X = O\cdot COCH_3$) gave an easy conversion, and hydrogen bromide (producing bromides, $X = Br$) gave exclusively cinnamyl bromide. The order of mobility, $OH < O\cdot COCH_3 < Br$, is that of increasing acidity of HX.

(*b*) The ionizing power of the medium (as indicated by its dielectric constant), e.g. benzonitrile > xylene.

(*c*) The capacity of the group R to supply electrons, thus conferring additional stability on the cation. Variation of R gave the order *p*-chlorophenyl > *p*-tolyl > phenyl > methyl > H.

Burton and Ingold's mechanism of anionotropic change was intended to apply primarily to transformations occurring in ionizing media,[72] and in solvents of poor ionizing power or in the absence of a solvent it is possible that the interconversion may occur without the separation of X:[73]

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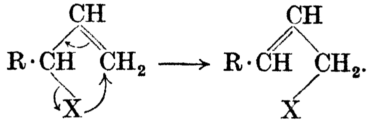
[71] *J.C.S.* 1928, 904, 1650.

[72] Compare the same authors' mechanism of addition to conjugated double linkages, Chap. XI, p. 149.



The two mechanisms are clearly the analogues of S_N1 and S_N2 for aliphatic substitution,[74] and their simultaneous operation may account for a 70 per cent. retention of optical activity in the change $C_6H_5\cdot CHX\cdot CH:CH\cdot CH_3 \rightarrow C_6H_5\cdot CH:CH\cdot CHX\cdot CH_3$ ($X = OH$ or o-$O\cdot CO\cdot C_6H_4\cdot COOH$), variation in the medium being without marked influence.[75]

Investigations of the replacement of the group X of an anionotropic system by a different group Y have also led to interesting results. The group Y may become linked either to the carbon atom from which X is removed, or to another carbon atom; further, the substitution may occur in one stage (II below) or by the addition of Y after removal of X (I). There are thus four possibilities, which may be represented as follows:

$$\left.\begin{array}{l} R\cdot CHX\cdot CH:CH_2 \rightarrow X^{\ominus} + R\cdot\overset{\oplus}{\overbrace{CH\cdot CH\cdot CH_2}} \\ Y^{\ominus} + R\cdot\overset{\oplus}{\overbrace{CH\cdot CH\cdot CH_2}} \begin{array}{l} \nearrow R\cdot CHY\cdot CH:CH_2 \\ \searrow R\cdot CH:CH\cdot CH_2Y \end{array} \end{array}\right\} \text{I}$$

$$Y^{\ominus} + R\cdot CHX\cdot CH:CH_2 \left.\begin{array}{l} \nearrow X^{\ominus} + R\cdot CHY\cdot CH:CH_2 \\ \searrow X^{\ominus} + R\cdot CH:CH\cdot CH_2Y \end{array}\right\} \text{II}$$

Since the formation of two isomerides by *either* mechanism (I or II) cannot be excluded, the isolation of a mixed product in these replacements must no longer be taken as proof of an ionization mechanism. Evidence of the two mechanisms is found in the observation that the reaction of hydrogen bromide, under standardized conditions, with $CH_3\cdot CH(OH)\cdot CH:CH_2$ and with the isomeride $CH_3\cdot CH:CH\cdot CH_2OH$, gives products containing *different* proportions of the isomeric bromides:[76] if substitution took place by the ionization mechanism alone, the mesomeric ion $CH_3\cdot\overbrace{CH\cdot CH\cdot CH_2}^{\oplus}$ would be formed initially in each case, and *identical* products would result. The analogy of these schemes with the two possible mechanisms of anionotropic change, and with the unimolecular and bimolecular mechanisms of aliphatic substitution is obvious.

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[73] Hughes, *Trans. Faraday Soc.* **1938, 34, 194.**

[74] See Chap. X.

[75] Kenyon, Partridge, and Phillips, *J.C.S.* 1937, 207.

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[76] Young and Lane, *J. Amer. Chem. Soc.* 1938, **60**, 847. Compare Arcus and Kenyon, *J.C.S.* 1938, 1912; Hughes, ref. 73.

XIII

MIGRATIONS FROM SIDE-CHAIN TO NUCLEUS AND OTHER REARRANGEMENTS

INVESTIGATIONS of the behaviour of aromatic compounds having atoms or groups linked to nitrogen in the side-chain have revealed a number of instances where, in the presence of acid, this group leaves the nitrogen and becomes attached to a carbon atom of the nucleus: $C_6H_5 \cdot NXR \rightarrow X \cdot C_6H_4 \cdot NHR$, where X is Halogen, NO_2, NO, OH, SO_3H, CH_3, NHC_6H_5, $N_2C_6H_5$, etc. In spite of the apparent similarity of these processes, however, there appear to be important differences in mechanism.

In several cases there is definite evidence that the change is *inter*molecular; the migrating group becomes detached from the molecule, and experimental proof of its freedom at some intermediate stage has been found. The necessity of an acid medium in these instances may arise from two factors: firstly, by co-ordination of the acid (electron-acceptor) with the nitrogen atom, the bond linking the mobile group may be weakened, and secondly, the production of the intermediate may demand the participation of a molecule of acid as a reagent. Certain important transformations involve the migration of an alkyl or acyl group from side-chain oxygen to nuclear carbon, and here again the catalyst may function by co-ordination; it probably forms a complex of the oxonium type. The majority of migrations from side-chain to nucleus appear to be *inter*molecular, but cases of truly *intra*molecular rearrangement nevertheless exist. The transformation here takes place within a single molecule, and the migrating group is never free; it comes within the sphere of influence of the nuclear carbon atom before its bond with the side-chain nitrogen (or oxygen) is ruptured. Sometimes, however, the evidence regarding mechanism is far from conclusive. Moreover, even if the transformation is known to be *inter*molecular, the nature of the intermediate may not be clear, while the exact manner in which an *intra*molecular change occurs is not always easy to determine. It is not surprising, therefore, that the literature should contain a large number of postulated schemes in which various intermediates appear, in addition to mechanisms of the *intra*molecular type.

A number of the more interesting examples of migration from side-chain to nucleus are dealt with below; for a more detailed treatment the reader is referred to one of the larger works on the subject. A short account of certain other rearrangements follows; these are mainly *intra*molecular changes.[1]

The Chloroamine Transformation. The transformations of aromatic chloroamines (a general term for compounds having chlorine attached to nitrogen) have been studied very fully. Acetylchloroaminobenzene (*N*-chloroacetanilide, $C_6H_5 \cdot NCl \cdot COCH_3$), prepared by the action of hypochlorite solutions on acetanilide,[2] is converted almost quantitatively by hydrochloric acid to a mixture of *o*- and *p*-chloroacetanilides (*C*-chloroacetanilides). Hydrochloric acid is the only agent which brings about the transformation,[3] and the proportions of the *o*- and *p*-isomerides produced are the same as in the direct chlorination of acetanilide.[4] Moreover, Orton and W. J. Jones[5] established the existence, in aqueous acetic acid solutions, of the equilibrium

$$C_6H_5 \cdot NCl \cdot COCH_3 + HCl \rightleftharpoons C_6H_5 \cdot NH \cdot COCH_3 + Cl_2,$$

and it is therefore clear that the 'chloroamine transformation' occurs in two stages, the chlorine formed in the above reversible process acting as a substituting agent,

$$Cl_2 + C_6H_5 \cdot NH \cdot COCH_3 = Cl \cdot C_6H_4 \cdot NH \cdot COCH_3 + HCl.$$

The formation of *o*- and *p*-chloroacetanilides is due to the *op*-directive influence of the acetylamino group. The whole series of reactions may be written as follows:

$$\begin{tikzcd}
C_6H_5 \cdot NCl \cdot COCH_3 + HCl \arrow[dr, shift left] & \\
& C_6H_5 \cdot NH \cdot COCH_3 + Cl_2. \arrow[ul, shift left] \arrow[dl] \\
Cl \cdot C_6H_4 \cdot NH \cdot COCH_3 + HCl &
\end{tikzcd}$$

The quantitative conversion of *N*-chloroacetanilide to the nuclear-substituted anilides depends upon the non-reversibility of the *C*-chlorination. A still more convincing proof of the two-stage mechanism is obtained from observations of the 'wandering' of the chlorine to a 'foreign' nucleus; a chloroamine in presence of hydrochloric acid forms an excellent chlorinating agent for anilines, anilides, and phenols.[6] This makes it evident that, at some stage of the process, the chlorine must be free; the transformation is thus definitely *inter*molecular. *N*-chloroacetanilide is also transformed to *o*- and *p*-chloroacetanilides by heating at 100°, and here again there is evidence that free chlorine appears at an intermediate stage.[7]

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[1] For more details of the subject up to 1927, and numerous references to the original papers, see Porter, *Molecular Rearrangements* (Chemical Catalog Co., New York, 1928). The later work is summarized by E. S. Wallis in Gilman's *Organic Chemistry* (John Wiley & Sons, New York, 1938), vol. 1, p. 720. A short account of recent advances may also be found in *Ann. Reports*, 1939, **36**, 191.

[2] Chattaway and Orton, *J.C.S.* 1899, **75**, 1046; 1901, **79**, 274.

[3] Armstrong, ibid. 1900, **77**, 1047.

[4] Orton and Bradfield, ibid. 1927, 986.

[5] Ibid. 1909, **95**, 1456; *Rep. Brit. Assoc.* 1910, p. 85. See also Orton, Soper, and Williams, *J.C.S.* 1928, 998.

As the result of this work of Orton and his collaborators, the chloroamine transformation in aqueous media has long been accepted as a typical *inter*molecular change. A recent investigation of the transformation of *N*-chloroacetanilide in 20 per cent. alcohol under the influence of radioactive hydrogen chloride (i.e. hydrochloric acid containing the radioactive isotope of chlorine)[8] has provided further confirmation;[9] the change in the radioactivity of the chloride ion in solution is in harmony only with an *inter*molecular mechanism for the transformation. The position is less simple than was formerly supposed, however, for there is a side reaction of considerable importance.[10] Moreover, in anhydrous solvents the change appears to take place by a different mechanism, for the work of Bell and his collaborators[11] has indicated that the transformations of *N*-chloroacetanilide, *N*-bromoacetanilide, *N*-iodoformanilide, and *N*-bromobenzanilide in *anhydrous* solvents (e.g. chlorobenzene, anisole) are one-stage *intra*molecular processes. The specific effect of halogen acids, observed in aqueous media, is here replaced by general acid catalysis, carboxylic acids and phenols being effective catalysts. Moreover, no free halogen could be detected in the system in the case of *N*-bromoacetanilide, while the iodination of formanilide by a small quantity of iodine present in the *N*-iodoformanilide solutions was shown to be far too slow to account for the rate of production of *p*-iodoformanilide.

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[6] Orton and King, ibid. 1911, **99**, 1185.

[7] Bradfield, ibid. 1928, 351.

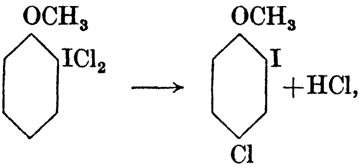
[8] The subject of induced radioactivity is dealt with in Glasstone, *Recent Advances in General Chemistry* (Churchill, 1936), p. 30.

[9] Olson, Porter, Long, and Halford, *J. Amer. Chem. Soc.* 1936, **58**, 2467; Olson, Halford, and Hornel, ibid. 1937, **59**, 1613. This is another example of the use of an isotopically distinguished element in the study of reaction mechanism. Compare Chap. IX.

[10] Olson and Hornel, *J. Org. Chem.* 1938, **3**, 76, and refs. there cited.

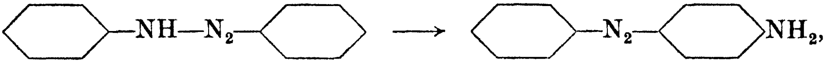
[11] *Proc. Roy. Soc.* 1934, **143** A, 377; 1935, **151** A, 211; *J.C.S.* 1936, 1154, 1520; **1939**, 1096, 1774.

Transformations of Aryl Iodide Dichlorides. The wandering of chlorine from *iodine* to nuclear carbon in the aryl iodide dichlorides is an *inter*molecular process. Thus *o*-iodoanisole dichloride is converted to 4-chloro-2-iodoanisole,



the chlorine substituting the hydrogen situated *para* to methoxyl, the more powerful of the two *op*-directing groups, and the chlorination of acetanilide by an aryl iodide dichloride has been accomplished.[12]

The Diazoamino-Aminoazo Conversion. Diazoaminobenzene, the product of the condensation of benzene diazonium chloride with aniline, is transformed, in presence of aniline hydrochloride, to *p*-aminoazobenzene,



the group $N_2C_6H_5$ migrating from side-chain nitrogen to nuclear carbon. In diazoaminotoluene, CH_3⬡—NH—N_2—⬡CH_3, the *p*-position is occupied, and in presence of *p*-toluidine hydrochloride a product having the migrating group *ortho* to NH_2 is obtained in small yield. On heating diazoaminotoluene with aniline or *o*-toluidine hydrochloride, however, the group migrates to the 'foreign' nucleus to give CH_3⬡—N_2—⬡NH_2 and CH_3⬡—N_2—$\underset{CH_3}{\text{⬡}}NH_2$ respectively,[13] a definite indication that the change is *inter*molecular. A study of the kinetics of the diazoaminobenzene transformation by Goldschmidt and Reinders[14] has shown that the velocity is proportional to the concentration of aniline hydrochloride, while if the hydrochloride be replaced by another aniline salt the speed varies with the strength of the combined acid; the participation of the free acid in the transformation is thus indicated.[12]

In a recent investigation, Kidd has been able to isolate aniline and benzeneazo-β-naphthol (the product of coupling benzenediazonium chloride with β-naphthol) in 90 per cent. of the theoretical quantities from an acidic solution of diazoaminobenzene,[15] while Rosenhauer and Unger find that the coupling of benzenediazonium chloride with aniline in neutral, feebly basic, or weakly acidic solutions proceeds by two independent routes, one leading to diazoaminobenzene and the other to *p*-aminoazobenzene.[16] Increasing acidity favours the latter, which becomes the exclusive product at a certain acid concentration. All these results lead to the conclusion that the conversion of diazoaminobenzene into *p*-aminoazobenzene proceeds through a fission of the molecule giving benzenediazonium chloride and aniline, followed by *p*-coupling, in accordance with a scheme such as the following:

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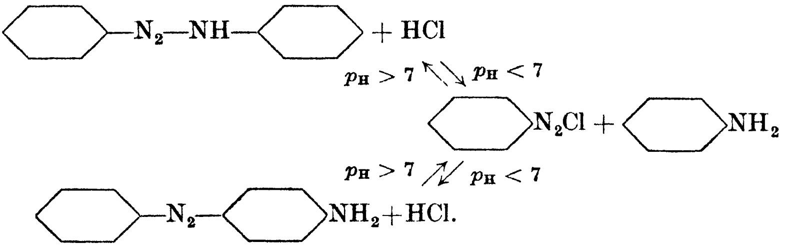
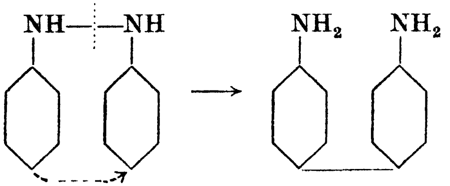
[12] Ingold, Smith, and Vass, *J.C.S.* 1927, 1245.

[13] Nietzki, *Ber.* 1877, **10**, 662.

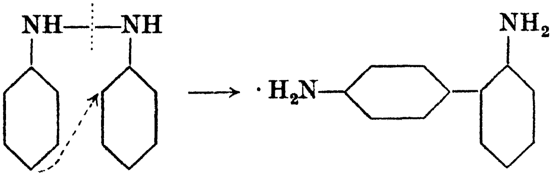
[14] Ibid. 1896, **29**, 1360, 1899.



*The Benzidine Transformation.** In contrast with the *inter*molecular processes described above, the rearrangements of diarylhydrazines (hydrazobenzenes) to give diphenyl derivatives, where the group —NHAr migrates, have been proved definitely to be *intra*molecular. Under the influence of acids, hydrazobenzene is transformed mainly to benzidine (4:4′-diaminodiphenyl),



At the same time some diphenyline (2:4′-diaminodiphenyl) is formed by *ortho*-migration:



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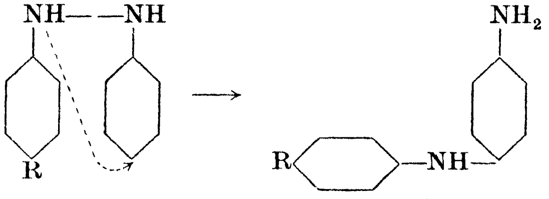
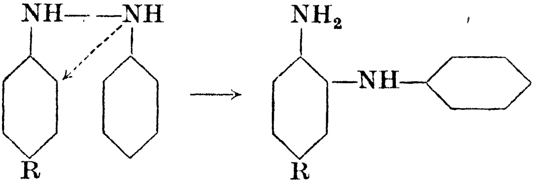
[15] *J. Org. Chem.* 1937, **2**, 198. Cf. Earl, *Chem. and Ind.* 1936, **55**, 192. [16] *Ber.* 1928, **61**, 392. Cf. Kidd, ref. 15; K. H. Meyer, *Ber.* 1921, **54**, 2265. * See p. 209.

When substituents are present in either or both nuclei, the benzidine conversion may be replaced, largely or completely, by other processes such as the transformation to *o*- and *p*-semidines, e.g.



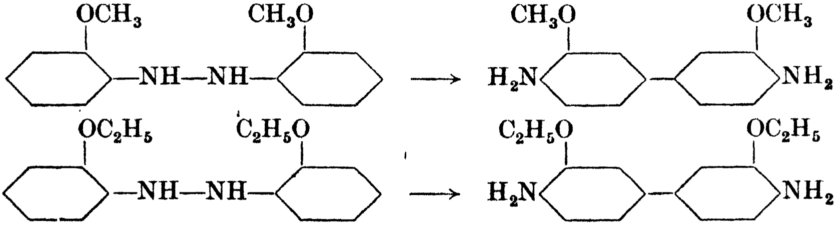
(*p*-semidine)



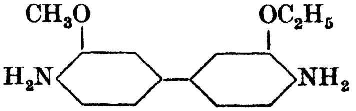
(*o*-semidine)

Various rearrangements may therefore occur simultaneously, leading to a mixed product, and the isomeric changes of a large number of hydrazobenzenes have been studied by Jacobsen and his co-workers.[17]

The compounds 2:2′-dimethoxy- and 2:2′-diethoxy-hydrazobenzene, however, undergo no rearrangement other than that of the benzidine type, and they change at comparable speeds. A study of the transformations of these compounds in the same solution has enabled Ingold and Kidd to demonstrate the truly *intra*molecular nature of this transformation.[18] Such a rearrangement would give rise to *two* products only, by the reactions



If, however, the migrating group were at any time free, the compound



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[17] Summarized in *Annalen*, 1922, **428**, 76.

[18] *J.C.S.* 1933, 984.

would be formed also. By a method of thermal analysis the product was shown to consist of *two* benzidines only, and positive evidence of the *intra*molecular character of the benzidine conversion was thus obtained. This means that the *p*-carbon atoms of the hydrazobenzene molecule come within each other's sphere of influence before the linkage of the nitrogens is broken. The —NHAr group is thus at no time free. It does not follow, of course, that the semidine conversions are *intra*molecular; they may proceed by a mechanism quite different from that of the benzidine rearrangement.

Transformations of Nitroamines. The transformations of aromatic nitroamines to nitroanilines have been studied by Orton and his collaborators.[19] The nitroamines are obtained[20] by treatment of the appropriate aniline with a mixture of nitric acid and acetic anhydride (the nitrating agent being acetyl nitrate, $CH_3 \cdot CO \cdot ONO_2$), and they are converted to *o*- and *p*-nitroanilines under the influence of *any* acid; the nitro group may even displace another group (e.g. Br) already present in the *o*- or *p*-position. There is actually some evidence of the migration of the group to a foreign nucleus, but, as Bradfield and Orton point out, 'no nitrating agent invariably and normally appears in the system in which a nitroamine is undergoing isomeric change, whereas the presence of chlorine can always be demonstrated during the isomeric change of a chloroamine'. They conclude that 'the facts are in harmony with the view that in the transformation of the nitroamines to nitroanilines an *intra*molecular process plays the important part'. The evidence is of a negative character, however; the criteria which have indicated that other processes are *inter*molecular are here absent, or almost so. If the migrating group were at any stage free, the tests to which the system has been subjected would almost certainly have revealed this fact clearly. Nevertheless the *intra*molecular character of the nitroamine transformation is not established so definitely as is the case with certain other rearrangements (the benzidine conversion, above, for example).

Transformations of Alkylanilines. The Hofmann-Martius rearrangement of alkylanilines[21] is a transformation of very considerable importance, since it provides an excellent method for preparing homologues of aniline. On heating the hydrochloride, hydrobromide, or hydriodide of an alkyl- or dialkyl-aniline or a phenyltrialkylammonium salt at 250°–350°, the alkyl groups migrate to the *o*- and *p*-positions in the nucleus. A similar transformation occurs if the amine is heated with certain metallic salts such as the chlorides of zinc, cadmium, or cobalt.[22] One, two, or three alkyl groups may thus be introduced into the nucleus. Different views have been held regarding the mechanism of the rearrangement, and both alkyl halides and olefins have been postulated as intermediates. Migration of the alkyl group to a foreign nucleus has been observed: thus, nuclear-alkylated alkylanilines have been found in the products of some rearrangements, and 2:4-dibenzylaniline is formed when *N*-benzylaniline is heated with cobalt chloride.[23]

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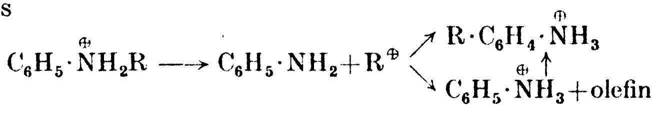
[19] *Rep. Brit. Assoc.* 1912, p. 117; Bradfield and Orton, *J.C.S.* 1929, 915, and references there cited.

[20] Orton, ibid. 1902, **81**, 806.

[21] *Ber.* 1871, **4**, 742, and later.

The most recent view, due to Hickinbottom,[24] is that the production of the nuclear-alkylated anilines involves the separation of the alkyl group as a positive ion; the formation of neutral radicals as intermediates is unlikely, since the known products of decomposition of these radicals have not been detected. On this view, olefins and alkyl halides, which are frequently found among the products, and which have been suggested as intermediates in the transformations, are the result of side reactions; thus, an olefin might arise from the loss of a proton by the positive alkyl group ($C_n H^{\oplus}_{2n+1} \rightarrow H^{\oplus} + C_n H_{2n}$). In the case of certain branched groups such as *iso*butyl, *tert*-butyl, and *iso*amyl, however, the formation of olefin appears to be of greater importance, and the rearrangement may here proceed largely through the attack of the olefin upon the nucleus,[25] a reaction which has been shown to occur.[26] The Hofmann-Martius rearrangement now becomes



$$\begin{tikzcd}
 & & R\cdot C_6H_4\cdot\overset{\oplus}{N}H_3 \\
C_6H_5\cdot\overset{\oplus}{N}H_2R \arrow[r] & C_6H_5\cdot NH_2+R^{\oplus} \arrow[ur] \arrow[dr] & \\
 & & C_6H_5\cdot\overset{\oplus}{N}H_3+\text{olefin} \arrow[uu]
\end{tikzcd}$$

and a metallic chloride will co-ordinate at the nitrogen in the same manner as the hydrogen ion does in the above representation. The necessity for postulating *two* routes is shown by the fact that whereas toluidines are formed in considerable quantities by heating methylaniline hydrobromide or hydriodide at 300° in open vessels, very little, if any, *p*-amino-*tert*-butylaniline is obtained by heating *tert*-

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[22] Reilly and Hickinbottom, *J.C.S.* 1920, **117**, 103.

[23] Hickinbottom, ibid. 1937, 1119.

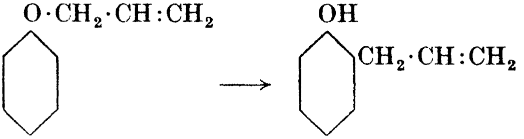
[24] Ibid. 1934, 1700.

[25] Ibid. 1931, 1281; 1932, 2396; 1937, 404.

[26] Ibid. 1935, 1279.

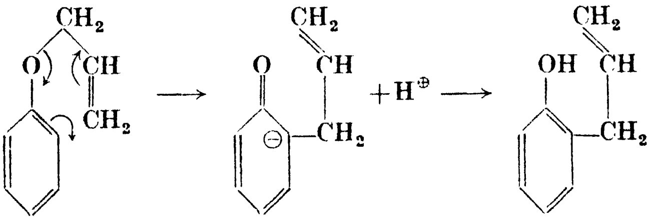
butylaniline hydrochloride at 212° or by heating the base with cobalt chloride under such conditions that volatile products can escape; high yields of butylene are formed, however.[25]

Rearrangements of Phenolic Ethers. Claisen has recorded[27] a number of examples of the formation of nuclear-alkylated phenols when allyl (and substituted allyl) aryl ethers are heated at about 200°. The allyl group migrates from side-chain oxygen to nuclear carbon, and takes up the *ortho*-position preferentially. Thus, phenyl allyl ether is transformed to *o*-allylphenol,



and no detectable quantity of *p*-allylphenol is formed.[28] The group becomes linked to the nucleus by the terminal (γ) carbon atom,[29] and the change is kinetically unimolecular.[30] Vinyl allyl ether, containing the essential part of the allyl aryl ether skeleton, undergoes a similar rearrangement to yield allylacetaldehyde.[31]

Demonstration of the *intra*molecular character of the migration of an allyl (or substituted allyl) group from oxygen to the *ortho*-carbon atom has been given by Hurd and Schmerling.[32] When a mixture of phenyl cinnamyl ether and β-naphthyl allyl ether was heated, each compound rearranged independently; there was no 'wandering' of the migrating group to the nucleus of the second compound. The thermal rearrangements of allyl aryl ethers to *o*-allyl phenols are therefore to be represented by a scheme such as the following:



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[27] *Ber.* 1912, **45**, 3157.

[28] Lauer and Leekley, *J. Amer. Chem. Soc.* 1939, **61**, 3042.

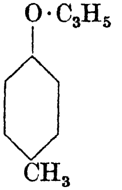
[29] Claisen and Tietze, *Ber.* 1925, **58**, 275; Hurd and Cohen, *J. Amer. Chem. Soc.* 1931, **53**, 1917.

[30] Kincaid and Tarbell, ibid. 1939, **61**, 3085; 1940, **62**, 728.

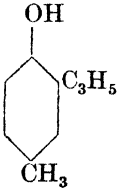
[31] Hurd and Pollack, ibid. 1938, **60**, 1905; *J. Org. Chem.* 1938, **3**, 550.

[32] *J. Amer. Chem. Soc.* 1937, **59**, 107.

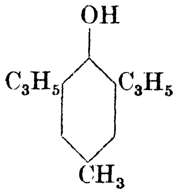
Such a mechanism would be possible only in a system which permits the electromeric changes indicated by the curved arrows, and it is in systems of this type that *ortho*-migration has been observed most frequently. If the *ortho*-positions are already occupied, however, the group takes up the *p*-position,[33] and the carbon which now becomes linked to the nucleus may be that which was originally attached to oxygen (the α-carbon).[34] The mechanism of this *para*-migration is clearly different from that of the *ortho*-rearrangement. If the *p*-position and both *o*-positions are occupied (as in 2:4:6-trialkylphenyl allyl ethers, for example), olefin is eliminated on heating, and, indeed, products which could arise only by an initial cleavage of the molecule have been found in some cases where the normal rearrangement occurs; e.g. in the rearrangement of (I) to (II) some (III) is formed;[35]



I



II



III

It is highly probable, therefore, that when the *p*-alkylated phenol is formed by rearrangement of the ether, the change is *inter*molecular, the migrating group being removed completely from the molecule and replaced at the *p*-position. The *ortho*-rearrangement of allyl aryl ethers, however, must be regarded as essentially *intra*molecular, with the possibility of an *inter*molecular process as a subsidiary change.

Several cases are on record in which a tertiary alkyl or a benzyl group migrates from oxygen to the nucleus under the action of heat. The electromeric changes depicted in the above scheme cannot occur here; the new linkage is formed by the carbon atom which was originally bound to oxygen, and it may take up either the *ortho*- or the *para*-position.[36,37] The migration of the benzyl group to a foreign nucleus has been observed in certain cases; thus, a mixture of benzyl phenyl ether and β-naphthol yields 1-benzyl-β-naphthol,[37] and when a solution of benzyl phenyl ether in quinoline is heated at 250°, benzylquinolines, phenoxyquinolines, phenol, and toluene are formed in addition to the normal products (*o*- and *p*-hydroxydiphenylmethanes).[38]

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[33] Claisen and Eisleb, *Annalen*, 1913, **401**, 21.

[34] Mumm and Möller, *Ber.* 1937, **70**, 2214. Compare Mumm *et al.*, ibid. 1939, **72**, 100.

[35] Hurd and Yarnall, *J. Amer. Chem. Soc.* 1937, **59**, 1686.

[36] Smith, ibid. 1933, **55**, 3718; Natelson, ibid. 1934, **56**, 1583.

[37] Behagel and Freiensehner, *Ber.* 1934, **67**, 1368.

There are also numerous instances in which phenyl alkyl ethers rearrange to alkylated phenols, not under the influence of heat alone, but in presence of a catalyst. The groups which migrate under these conditions include *iso*propyl, *iso*butyl, and *sec*-butyl, but not *n*-alkyl groups. The catalysts which promote these changes are hydrogen chloride, sulphuric acid, zinc chloride, boron fluoride, and aluminium chloride. The migrating group may enter either the *ortho*- or the *para*-position, and the atom severed from oxygen becomes attached to the nucleus. Sometimes the group itself undergoes isomeric change during the process (e.g. *iso*butyl → *tert*-butyl). In a number of these catalysed rearrangements, the migration of the group to a foreign nucleus has been observed; for example, when boron fluoride is passed into phenyl *iso*propyl ether the product contains phenol and alkylated ethers in addition to alkylated phenols,[39] under the influence of zinc chloride the benzyl group migrates from benzyl phenyl ether to anisole,[40] and phenyl and *p*-tolyl *iso*propyl ethers on treatment with aluminium chloride in presence of diphenyl ether give alkylated diphenyl ethers.[41] There can be no doubt that all these catalysed rearrangements, and also those of benzyl and *tert*-alkyl aryl ethers under the influence of heat alone, are *inter*molecular.

It is less easy to draw conclusions regarding the form in which the group migrates, but Hickinbottom finds that, on heating benzyl phenyl ether in quinoline solution, the benzyl and phenoxy-groups attack the same position of the quinoline nucleus; this makes it unlikely that they react as oppositely charged ions, but is consistent with the view that the ether dissociates into neutral radicals.[38]

Transformations of Phenolic Esters (*Fries Reaction*). The acyl group of a phenol ester migrates to the nucleus when the compound is treated with aluminium chloride, zinc chloride, or ferric chloride, the product being an *o*- or *p*-hydroxy-aromatic ketone. This is known as the Fries Reaction, and is exemplified by the conversion of phenyl acetate to *o*-hydroxyacetophenone,

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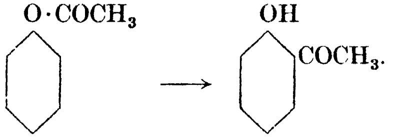
[38] Hickinbottom, *Nature*, 1938, **142**, 830; 1939, **143**, 520.

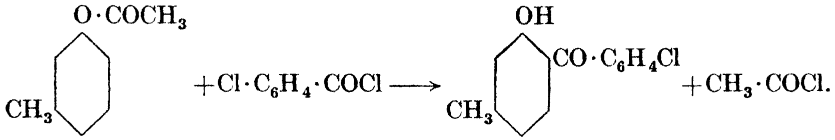
[39] Sowa, Hinton, and Nieuwland, *J. Amer. Chem. Soc.* 1932, **54**, 2019; 1933, **55**, 3402.

[40] Short and Stewart, *J.C.S.* 1929, 553.

[41] Smith, *J. Amer. Chem. Soc.* 1934, **56**, 717.



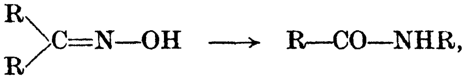
Fries, von Auwers, and their co-workers, who have studied numerous reactions of this type, consider the rearrangement to be *intra*molecular.[42] There is evidence, however, that the acyl group becomes free during the course of the transformation. Thus, treatment of a mixture of *m*-tolyl acetate and *m*-chlorobenzoyl chloride with zinc chloride yields a derivative of benzophenone, acetyl chloride being displaced:[43]



Cox finds, too, that if the reaction is carried out in diphenyl ether as solvent, the acyl group migrates to the ether, while in presence of alcohol the ethyl ester is formed.[44]

The Beckmann Rearrangement

The transformation of an oxime into an acid amide,



$$R_2C{=}N{-}OH \longrightarrow R{-}CO{-}NHR,$$

was first observed by Beckmann in 1886.[45] It occurs under the influence of a number of reagents, which include phosphorus pentachloride and oxychloride, sulphuric acid, hydrochloric acid, acetyl and benzenesulphonyl chlorides, and the chlorides of antimony and of a number of metals. The majority of ketoximes undergo this rearrangement, and also the *N*-ethers of aldoximes and sometimes aldoximes themselves; in certain rather rare cases an abnormal rearrangement occurs.[46]

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[42] Fries *et al.*, *Ber.* 1908, **41**, 4272, and later; von Auwers *et al.*, *Annalen*, 1926, **447**, 162; 1928, **460**, 240; **464**, 293; *Ber.* 1928, **61**, 1495.

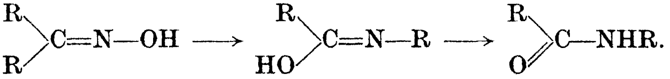
[43] Skraup and Poller, ibid. 1924, **57**, 2033. Compare Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56.

[44] *J. Amer. Chem. Soc.* 1930, **52**, 352 (this paper contains a useful summary of suggested mechanisms).

[45] *Ber.* 1886, **19**, 988.

The existence of unsymmetrical ketoximes in two forms was interpreted by Hantzsch and Werner as an instance of geometrical isomerism.[47] The isomeric ketoximes rearrange to give different amides, and it was assumed that a *cis* interchange of groups occurred. The configurations of the oximes were then deduced from the nature of the products, on the basis of this assumption.[48] The postulate of a *cis* interchange rested on no experimental foundation, however, and more recent work has shown that *trans* interchange takes place usually if not invariably.[49] Mills has pointed out, indeed, that *trans* exchange is probable on stereochemical grounds,[50] and any complete theory of the mechanism of the Beckmann Rearrangement must be applicable to such exchange.

Beckmann himself regarded the transformation as involving an exchange of positions by the alkyl and hydroxyl groups, giving the 'pseudo' form of the amide, followed by the migration of hydrogen:[51]



$$\overset{R}{\underset{R}{>}}C{=}N{-}OH \longrightarrow \overset{R}{\underset{HO}{>}}C{=}N{-}R \longrightarrow \overset{R}{\underset{O}{>}}C{-}NHR.$$

Nothing is here postulated concerning the mechanism by which the actual interchange occurs. Lachman suggested later that the process takes place in the ion of the hydrochloride or other salt of the oxime, a view which was confirmed by his observation of the rearrangement of benzophenoneoxime in aqueous hydrochloric acid.[52] On the other hand, an investigation of the transformations of acyl derivatives (esters) of oximes led Kuhara to the conclusion that these substances (or their salts) were the entities which were capable of rearrangement.[53]

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[46] For an excellent summary of the literature relating to the Beckmann Rearrangement up to 1932, see Blatt, *Chem. Reviews*, 1933, **12**, 215.

[47] *Ber.* 1890, **23**, 11. See Chap. XIV.

[48] Hantzsch, *Ber.* 1891, **24**, 13, 51.

[49] Meisenheimer, ibid. 1921, **54**, 3206, and later. The evidence is summarized in Chap. XIV.

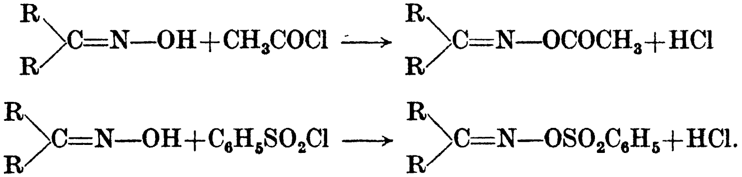
[50] Presidential Address to Brit. Assoc., 1932; *Chem. and Ind.* 1932, **51**, 750.

[51] *Ber.* 1894, **27**, 300.

[52] *J. Amer. Chem. Soc.* 1924, **46**, 1477; 1925, **47**, 260. Stieglitz had previously postulated salt-formation (ibid. 1914, **36**, 272).

[53] M. Kuhara, *On the Beckmann Rearrangement* (Imperial University of Kyoto, Tokio, 1926). Sluiter made a similar suggestion at an earlier date (*Rec. trav. chim.* 1905, **24**, 372), but without experimental justification.

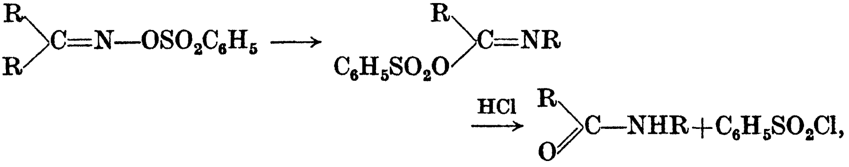
Kuhara found that the speed of rearrangement of benzophenoneoxime under the influence of different acid chlorides varied in the same order as the electron-attractive character of the acyl group as indicated by the dissociation constant of the corresponding acid, e.g. $C_6H_5 \cdot SO_2Cl > CH_2Cl \cdot COCl > CH_3 \cdot COCl$. Moreover, while the presence of hydrogen chloride was necessary to promote the rearrangement of the acetate of the oxime, the benzenesulphonate rearranged on melting and even on standing. An *alkaline* solution of benzophenoneoxime, in fact, rearranged on treatment with benzenesulphonyl chloride. The transformation of an oxime was ascribed, therefore, to the formation of an ester, e.g.



$$\begin{matrix}R\\R\end{matrix}\!\!>C{=}N{-}OH + CH_3COCl \longrightarrow \begin{matrix}R\\R\end{matrix}\!\!>C{=}N{-}OCOCH_3 + HCl$$

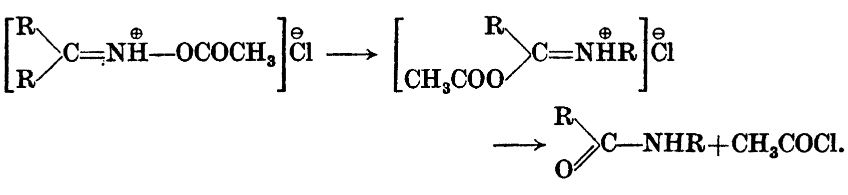
$$\begin{matrix}R\\R\end{matrix}\!\!>C{=}N{-}OH + C_6H_5SO_2Cl \longrightarrow \begin{matrix}R\\R\end{matrix}\!\!>C{=}N{-}OSO_2C_6H_5 + HCl.$$

If this is the ester of a strong acid (e.g. benzenesulphonic), it rearranges spontaneously,



$$\begin{matrix}R\\R\end{matrix}\!\!>C{=}N{-}OSO_2C_6H_5 \longrightarrow \begin{matrix}R\\C_6H_5SO_2O\end{matrix}\!\!>C{=}NR \xrightarrow{HCl} \begin{matrix}R\\O\end{matrix}\!\!>C{-}NHR + C_6H_5SO_2Cl,$$

whereas the ester of a weak acid rearranges only in the form of its ion:



$$\left[\begin{matrix}R\\R\end{matrix}\!\!>C{=}\overset{\oplus}{N}H{-}OCOCH_3\right]\overset{\ominus}{Cl} \longrightarrow \left[\begin{matrix}R\\CH_3COO\end{matrix}\!\!>C{=}\overset{\oplus}{N}HR\right]\overset{\ominus}{Cl} \longrightarrow \begin{matrix}R\\O\end{matrix}\!\!>C{-}NHR + CH_3COCl.$$

The spontaneous transformation of the derivatives of oximes with strong acids has been confirmed by Chapman, in a study of oxime picryl ethers, $\begin{matrix}R\\R\end{matrix}\!\!>C{=}N{-}OC_6H_2(NO_2)_3$. These rearrange on heating without the intervention of a catalyst, the change being unimolecular. There is no evidence of dissociation into ions, and Chapman, like Kuhara, concludes that the reagents which normally bring about the Beckmann Transformation give rise to such derivatives, which then undergo spontaneous intramolecular rearrangement.[54] The effect of hydrogen chloride was difficult to reconcile with this view, since Stieglitz and Peterson had found that the ester $CR_2{=}NCl$ does not rearrange,[55] and Chapman therefore carried out a thorough examination of the transformation of benzophenoneoxime,

$$(C_6H_5)_2C{=}N{-}OH \longrightarrow C_6H_5CO{-}NHC_6H_5,$$

in ethylene dichloride solutions of hydrogen chloride.[56] He found that an initial period of low velocity was followed by a rapid change at almost constant speed; autocatalysis was thus indicated. The presence of benzanilide (the reaction product) reduced the initial slow period, which was completely removed by the introduction of a very small quantity of the imidochloride of the anilide, $C_6H_5CCl{=}NC_6H_5$ (the chloride of the 'pseudo' form). The presence of hydrogen chloride was necessary, however, in addition to the imidochloride. Chapman's results will be best understood by reference to Fig. 18, which is reproduced from his paper. He concludes therefrom that the Beckmann Rearrangement of benzophenoneoxime in presence of hydrogen chloride involves the following series of changes: (*a*) production of a small quantity of benzanilide (slow change),

$$(C_6H_5)_2C{=}N{-}OH \longrightarrow C_6H_5CO{-}NHC_6H_5;$$

(*b*) reaction of benzanilide with hydrogen chloride to give the imidochloride,

$$C_6H_5CO{-}NHC_6H_5+HCl \longrightarrow C_6H_5CCl{=}NC_6H_5+H_2O;$$

(*c*) condensation of oxime and imidochloride,

$$(C_6H_5)_2C{=}N{-}OH+C_6H_5CCl{=}NC_6H_5 \longrightarrow (C_6H_5)_2C{=}N{-}OC(C_6H_5){=}NC_6H_5+HCl;$$

(*d*) conversion of this oxime ether to cation,

$$(C_6H_5)_2C{=}N{-}OC(C_6H_5){=}NC_6H_5+H^{\oplus} \longrightarrow (C_6H_5)_2C{=}N{-}OC(C_6H_5){=}\overset{\oplus}{N}HC_6H_5.$$

The positive charge on this cation will have the effect of rendering the ether group $-OC(C_6H_5){=}\overset{\oplus}{N}HC_6H_5$ electron-attractive, like the anion of a strong acid. Chapman confirmed the above mechanism by the preparation and examination of the condensation product from benzophenoneoxime and benzanilideimidochloride; when treated with aqueous hydrogen chloride it was converted quantitatively to benzanilide, and it also catalysed the rearrangement of the oxime to the same extent as an equivalent quantity of benzanilideimidochloride. The rapid rearrangement brought about by hydrogen chloride is thus capable of interpretation as due to the spontaneous transformation of an oxime derivative which is of the same type as the derivatives formed with strong acids, and hence hydrogen chloride falls into line with the other reagents. There remains, of course, the slower change by which the first small quantity of anilide is formed, and Chapman ascribes this to a far less rapid rearrangement of the *salt*. Nevertheless, the transformation proceeds mainly through the intermediate formation of an ester-like compound which is capable of undergoing spontaneous rearrangement.

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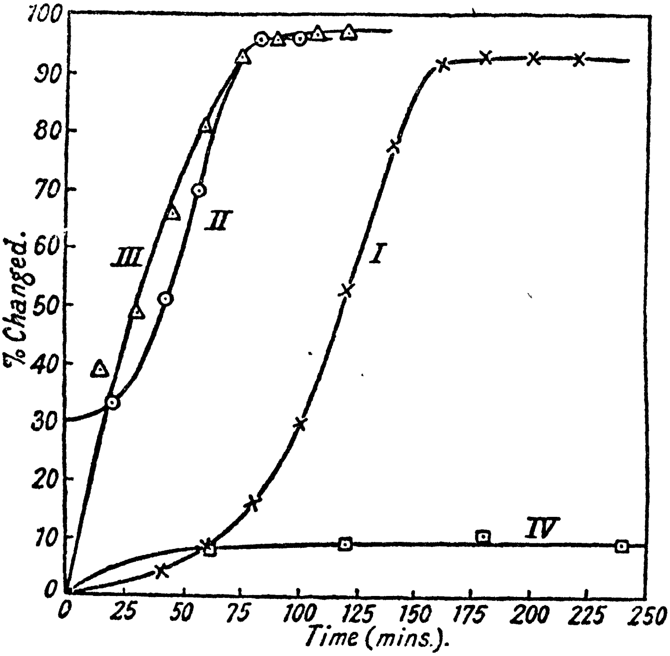
[54] *J.C.S.* 1933, 806; 1934, 1550; 1936, 448.

[55] *Ber.* 1910, **43**, 782.

[56] *J.C.S.* 1935, 1223.



I. 0·42 *Mol.* HCl: *starting from pure oxime.*
II. 0·42 *Mol.* HCl: *starting from* 30% *anilide,* 70% *oxime.*
III. 0·41 *Mol.* HCl + 0·002 *mol. benzanilideimidochloride.*
IV. 0·002 *Mol. benzanilideimidochloride.*

Fig. 18. Velocity of the Beckmann Transformation of benzophenoneoxime. Effect of hydrogen chloride as catalyst. (Reproduced from Chapman, *J.C.S.* 1935, 1224.)

Chapman's work upon the Beckmann Transformation of oxime ethers has also provided important information concerning the effect of changes in the solvent and in the concentration and chemical character of the ether. His results are as follows:

(1) Solvents of high dipole moment increase the velocity. Thus, in different media, the speeds are in the order $CCl_4 < CHCl_3 < C_2H_4Cl_2$, while addition of other solvents to carbon tetrachloride increased the velocity in the order

$$C_6H_{14}(\mu = 0) < C_6H_5Cl(\mu = 1{\cdot}5) < C_2H_4Cl_2(\mu = 1{\cdot}8)$$
$$< CH_3{\cdot}CO{\cdot}CH_3(\mu = 2{\cdot}8) < CH_3{\cdot}NO_2(\mu = 3) < CH_3{\cdot}CN(\mu = 3{\cdot}4).$$

(2) Increase in the initial concentration of ether produces more than a proportionate increase in speed. The ether thus appears to act catalytically, and, since the unimolecular velocity coefficient remained constant throughout any one experiment, the same must apply to the product. This may be a medium effect similar in nature to (1).

(3) Electron-repulsive substituents in the R groups of $CR_2{=}NOX$ increase the speed of transformation, and vice versa; this is more pronounced when the substituent is in the migrating group than when it is in the other.

(4) Electron-attractive substituents in the group X increase the ease of rearrangement. Thus, while the 2:4-dinitrophenyl ether of benzophenoneoxime [$X = C_6H_3(NO_2)_2$] does not rearrange at 100°, the picryl ether [$X = C_6H_2(NO_2)_3$] changes at temperatures as low as 40°.

These observations throw some light upon the actual mechanism by which the oxime derivative undergoes transformation. It has already been pointed out that there is no reason to suppose that the migrating groups are at any time free, a view which is now confirmed by the retention of optical activity in the transformation of methyl γ-heptyl ketoxime.[57] Mechanisms dependent upon the withdrawal of water to give a cyclic[58] or a univalent nitrogen compound[59] are further inadmissible, since they are not applicable to the transformation of the aldoxime *N*-ethers[60] or to the Beckmann change in aqueous solutions, and suffer from various other disadvantages.[46]

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[57] Kenyon and Young, *J.C.S.*, 1941, 263.

[58] Wallach, *Annalen*, 1906, **346**, 272.

[59] Stieglitz, *Amer. Chem. J.*, 1896, **18**, 751.

[60] Brady and Dunn, *J.C.S.*, 1926, 2411.

A survey of the whole position indicates that the actual transformation may occur in an ester (or similar derivative), or in a salt of the oxime or of its ester. The rearrangement of esters is demonstrated by the work of Kuhara and Chapman. The observation, by the former, that the presence of hydrogen chloride is necessary for the transformation of an acetate, but not of a benzenesulphonate, indicates further that an oxime ester of a weak acid can rearrange only as salt. Chapman has shown, moreover, that the rearrangement when catalysed by hydrogen chloride does not proceed *entirely* through an ester-like intermediate, while salt-formation must occur when an oxime changes in an aqueous solution of hydrochloric acid, as observed by Lachman. Again, it is not easy to visualize the formation of esters by the *N*-ethers of aldoximes, and it is significant that the corresponding *O*-ethers, which have no basic characters, do not undergo rearrangement.[59]

It seems simplest to suppose[61] that the rearrangement is made possible by the tendency of the group OX to dissociate as anion (in esters of strong acids), *or* by the electron-attraction of a co-ordinated proton (in salts),[62] *or* by both (in salts of esters). In some cases all of these may contribute to the complete rearrangement. Electrons are thus drawn away from the nitrogen atom (process *a* below), and the electromeric change *b* thereby initiated. Clearly, the more powerful the electron attraction of OX and the greater the ionizing influence of the medium, the greater will be the tendency for process *b* to occur; it will also be facilitated by electron-repulsion in the R groups. All these deductions are in harmony with the facts. When change *b* has been initiated (but *not completed*, since the free rotation about the single bond so created would lead to an identical product from stereoisomeric oximes[63]), the molecule is in an activated state, and the actual rearrangement occurs as the result of several further processes which are probably simultaneous. R comes under the influence of the nitrogen atom (process *c*, where the arrow indicates the reaction of the nitrogen electrons with R, and not the movement of R), and begins to relinquish the electron pair linking it to carbon

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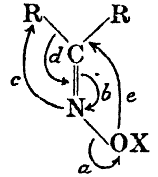
[61] This is probably an expression, in other terms, of previous views such as those of Bücherer, Biltz, Meisenheimer, and Ramart-Lucas (see ref. 46). Cf. also Chapman, *J.C.S.* 1936, 450.

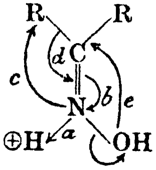
[62] It seems unnecessary to assume that the proton is effective only when co-ordinated with oxygen of OH or OX (cf. Chapman, *J.C.S.* 1935, 1226).

[63] Compare Montagne's criticism of Stieglitz's univalent nitrogen theory, *Ber.* **1910**, **43**, 2014.

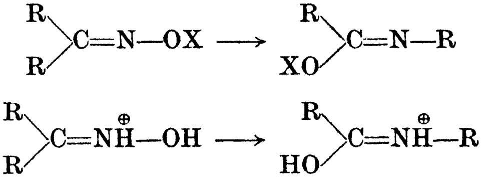
(process *d*), this being facilitated by electron-repulsive substituents in R; substituents in the migrating group therefore have a greater effect than similar substituents in the other group. At the same time, the hydroxyl or OX group comes under the influence of carbon (process *e*; this group moves with its electrons), and continues the process of breaking away from nitrogen. The completion of these various processes gives the rearrangement of I and II to III and IV; if X is the anion of a weak acid, the combination of both the processes marked *a* is necessary.

I. (ester)





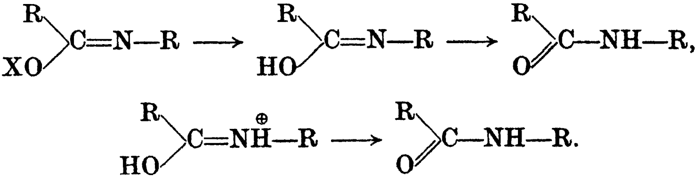
II. (salt)



I. $\mathrm{R(R)C{=}N{-}OX \longrightarrow R(XO)C{=}N{-}R}$ III.

II. $\mathrm{R(R)C{=}\overset{\oplus}{N}H{-}OH \longrightarrow R(HO)C{=}\overset{\oplus}{N}H{-}R}$ IV.

Hydrolysis of III and loss of proton from IV give the amides which are the ultimate products:



$$\mathrm{R(XO)C{=}N{-}R \longrightarrow R(HO)C{=}N{-}R \longrightarrow R(O{=})C{-}NH{-}R,}$$

$$\mathrm{R(HO)C{=}\overset{\oplus}{N}H{-}R \longrightarrow R(O{=})C{-}NH{-}R.}$$

The Hofmann, Lossen, and Curtius Degradations[64]

These processes lead to the production of amines from acid amides ($\mathrm{R{\cdot}CO{\cdot}NH_2}$), hydroxamic acids ($\mathrm{R{\cdot}CO{\cdot}NHOH}$ or a derivative $\mathrm{R{\cdot}CO{\cdot}NHOX}$), and acid azides ($\mathrm{R{\cdot}CO{\cdot}N_3}$, acyl derivatives of hydrazoic acid) respectively. In each case an isocyanate has been shown to be an intermediate,[65] and the formation of this compound involves the migration of an alkyl group from carbon to nitrogen. The processes may be written as follows:

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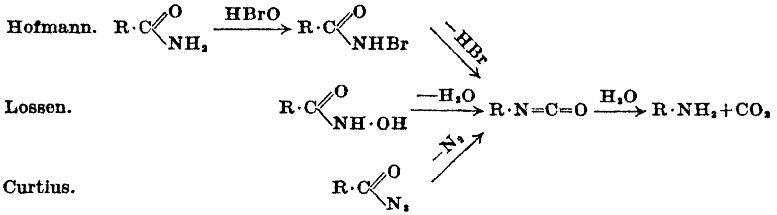
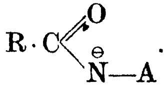
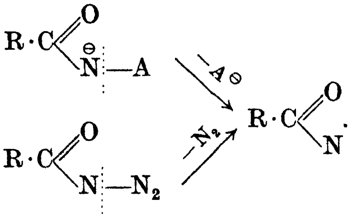
[64] Hofmann, *Ber.* 1882, **15**, 407; Lossen, *Annalen*, 1877, **186**, 1; Curtius, *J. pr. Chem.* 1901, **63**, 428.

[65] Hofmann, ref. 64; Tiemann, *Ber.* 1891, **24**, 4162; Mauguin, *Compt. rend.* 1909, **149**, 790; Schroeter, *Ber.* 1909, **42**, 2336, 3356; Forster, *J.C.S.* 1909, **95**, 433.



In contrast with the Beckmann Transformation, which is brought about by acidic reagents, these processes take place in alkaline solutions and under these conditions the bromoamide of the Hofmann change and the hydroxamic acid of the Lossen change are present as salts with anions of the general formula  $R\cdot C{\scriptstyle\diagup}^{O}_{\diagdown \overset{\ominus}{N}-A}$. According to Whitmore, who has put forward a scheme by which these and certain other transformations may be represented,[66] the anion loses the atom or group A with a complete octet of electrons, leaving the nitrogen with an incomplete electronic group (sextet), and the acid azide of the Curtius degradation similarly loses a nitrogen molecule. This step may therefore be written



Whitmore's view is supported by the observation, made by Hauser and his collaborators,[67] that when a series of dibenzhydroxamic acids $C_6H_5\cdot CO\cdot NH\cdot O\cdot CO\cdot C_6H_4X$ are rearranged in aqueous ammonia, the logarithms of the velocity coefficients bear a linear relationship to the values of $\log K$ for the corresponding benzoic acids $HO\cdot CO\cdot C_6H_4X$. While electron-attractive characters in the substituent X thus facilitate the rearrangement, however (as they facilitate ionization of the acid), the reverse is the case in the corresponding change of a series of hydroxamic acids $X \cdot C_6H_4 \cdot CO \cdot NH \cdot O \cdot CO \cdot C_6H_5$ and also in the Hofmann degradation of a series of bromoamides $X \cdot C_6H_4 \cdot CO \cdot NHBr$.

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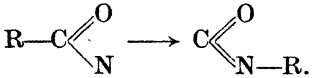
[66] *J. Amer. Chem. Soc.* 1932, **54**, 3274.

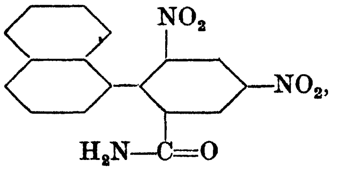
[67] Ibid. 1937, **59**, 121, 2308; 1939, **61**, 618.

The next step is the rearrangement of the residue to give an isocyanate, the group R migrating from carbon to nitrogen,



There is considerable evidence of a stereochemical character that this is an *intra*molecular change. If R is an optically active group, linked to the remainder of the molecule by the asymmetric carbon atom, asymmetry will be lost, largely or completely, if it becomes free at any stage.[68] An almost quantitative retention of optical activity has been found by Kenyon, however, when hydratropamide,

$\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!CH \cdot CONH_2$, and hydratropic azide undergo degradation,[69, 57] and Wallis and co-workers have observed a complete absence of racemization during the Curtius, Hofmann, and Lossen degradations of optically active derivatives of benzylmethylacetic acid, the rotation of the amines obtained from azide, bromoamide, and hydroxamate being identical.[70] A complete preservation of optical activity is also found during the Hofmann degradation of the compound



where asymmetry is due to restricted rotation, and where dissociation at any stage would have made free rotation possible with the consequent formation of a racemic product.[71] Finally, a quantitative yield of *tert*-butylmethylamine (*neo*pentylamine) is obtained from *tert*-butylacetamide,[72] whereas reactions in which dissociation occurs invariably lead to *tert*-amyl derivatives by rearrangement of the group,[73] and only one isocyanate is produced when benzylmethylacetazide is degraded in presence of triphenylmethyl radicals.[74] There can, then, be no doubt regarding the *intra*molecular character of the migration of the group R from carbon to nitrogen; the group is not free at any stage. Whitmore suggests[66] that this group migrates with its electron pair, but such a process is difficult to visualize without postulating its freedom for an instant of time, and it seems more probable that the binding of R by the unshared electrons of the nitrogen and the release of a pair by R to carbon occur simultaneously. These electronic movements may be written

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[68] Compare p. 126.

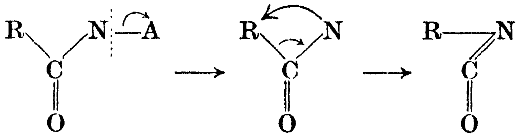
[69] Arcus and Kenyon, *J.C.S.*, 1939, 916.

[70] *J. Amer. Chem. Soc.* 1926, **48**, 169; 1931, **53**, 2787; 1933, **55**, 1701.

[71] Ibid. 1933, **55**, 2598. Optical activity due to restricted rotation is dealt with in Chap. XIV.

[72] Whitmore and Homeyer, *J. Amer. Chem. Soc.* 1932, **54**, 3435.

[73] Whitmore *et al.*, ibid. 1932, **54**, 3431; 1939, **61**, 1586.



This is similar to the mechanism suggested above for the Beckmann rearrangement,[75] where, however, the group A does not leave the molecule. These rearrangements have one feature in common; the group R migrates to an atom which has unshared electrons, and it is easy to envisage its attachment by these electrons as occurring simultaneously with the release of the pair by which it was linked originally.

Rearrangements of Imino-ethers and Amidines

The imino-aryl ethers, $\mathrm{Ar{\cdot}C}\langle{}^{\mathrm{NAr}}_{\mathrm{OAr}}$, derivatives of the ‘pseudo’ forms of acid amides, are transformed at temperatures above 220° to isomeric derivatives of the ‘normal’ acid amides, $\mathrm{Ar{\cdot}C}\langle{}^{\mathrm{NAr_2}}_{\mathrm{O}}$. Prototropic change in the amido-imidol system,

$$\mathrm{HO{-}}\underset{|}{\mathrm{C}}{=}\underset{|}{\mathrm{N}} \rightleftarrows \mathrm{O{=}}\underset{|}{\mathrm{C}}{-}\underset{|}{\mathrm{N}}\mathrm{H},$$

has long been recognized (e.g. in simple acid amides, uric acid, cyanic acid),[76] and the rearrangement of the imino-aryl ethers involves the migration of an aryl group in the same system,

$$\mathrm{ArO{-}}\underset{|}{\mathrm{C}}{=}\underset{|}{\mathrm{N}} \longrightarrow \mathrm{O{=}}\underset{|}{\mathrm{C}}{-}\underset{|}{\mathrm{N}}\mathrm{Ar}.$$

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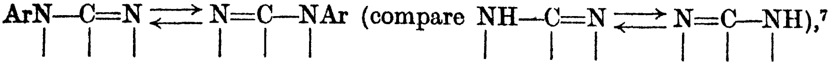
[74] Wallis, ibid. 1929, **51**, 2982.

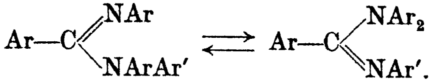
[75] Resemblances between these processes and the Beckmann rearrangement were pointed out by Stieglitz, who represented them by his univalent nitrogen mechanism (*Amer. Chem. J.* 1896, **18**, 751; 1903, **29**, 49. Compare Jones, ibid. 1912, **48**, 1).

[76] See Baker, *Tautomerism* (Routledge & Sons, 1934), pp. 136 ff.

A similar rearrangement occurs in the amidine system,

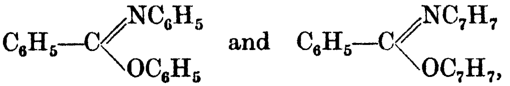


$\mathrm{Ar}\underset{|}{\mathrm{N}}{-}\underset{|}{\mathrm{C}}{=}\underset{|}{\mathrm{N}} \rightleftarrows \underset{|}{\mathrm{N}}{=}\underset{|}{\mathrm{C}}{-}\underset{|}{\mathrm{N}}\mathrm{Ar}$ (compare $\underset{|}{\mathrm{N}}\mathrm{H}{-}\underset{|}{\mathrm{C}}{=}\underset{|}{\mathrm{N}} \rightleftarrows \underset{|}{\mathrm{N}}{=}\underset{|}{\mathrm{C}}{-}\underset{|}{\mathrm{N}}\mathrm{H}$),[77] as in



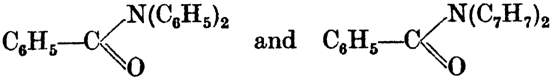
$$\mathrm{Ar{-}C}\begin{cases}\mathrm{=NAr}\\ \mathrm{-NArAr'}\end{cases} \rightleftarrows \mathrm{Ar{-}C}\begin{cases}\mathrm{-NAr_2}\\ \mathrm{=NAr'}.\end{cases}$$

These transformations have been studied by Chapman.[78] While the amidine rearrangement is reversible, the same equilibrium mixture being obtained by heating either isomeride at a temperature exceeding 300°, the imino-ether transformation goes to completion as far as can be ascertained; if it is reversible, the amount of imino-ether present at equilibrium is too small for detection. The corresponding imino-*thio*ethers, however, appear to rearrange reversibly.[79] The velocities of the transformations were measured by determination of the proportions of the isomerides, after heating for definite time intervals, by thermal analysis. The changes were shown to be unimolecular. Their *intra*molecular character was demonstrated by heating a mixture of two imino-ethers or amidines at the temperature at which rearrangement occurs. Under these conditions, the ethers

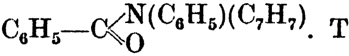


$$\mathrm{C_6H_5{-}C}\begin{cases}\mathrm{=NC_6H_5}\\ \mathrm{-OC_6H_5}\end{cases} \quad\text{and}\quad \mathrm{C_6H_5{-}C}\begin{cases}\mathrm{=NC_7H_7}\\ \mathrm{-OC_7H_7},\end{cases}$$

for example, gave the two products



$$\mathrm{C_6H_5{-}C}\begin{cases}\mathrm{-N(C_6H_5)_2}\\ \mathrm{=O}\end{cases} \quad\text{and}\quad \mathrm{C_6H_5{-}C}\begin{cases}\mathrm{-N(C_7H_7)_2}\\ \mathrm{=O}\end{cases}$$

and no trace of the mixed product  $\mathrm{C_6H_5{-}C}\begin{cases}\mathrm{-N(C_6H_5)(C_7H_7)}\\ \mathrm{=O}\end{cases}$. There was no interchange of groups; the rearrangements of the ethers occurred independently, and hence the migrating group was not at any stage free, in contrast with prototropic changes in the same systems.

The transformations of both imino-ethers and amidines are facilitated by electron-attractive substituents in the migrating nucleus, and by electron-repulsive substituents in the other aryl groups. All these facts, together with the results of observations of the equilibrium positions for various amidines, are in harmony with a mechanism similar to that suggested above for the Beckmann and other transformations; it may be written as follows:[80]

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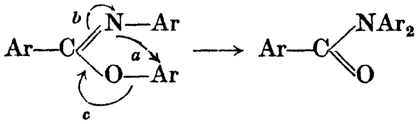
[77] Ibid., p. 140.

[78] *J.C.S.* 1925, **127**, 1992; 1927, 1743; 1929, 2133; 1930, 2458, 2462.

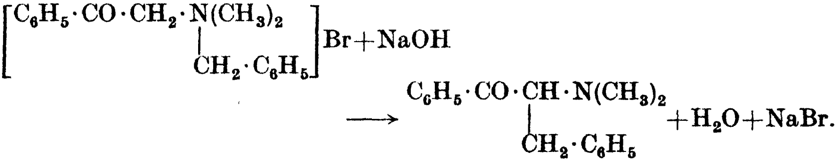
[79] Ibid. 1926, 2296.



(in the amidine transformation, OAr is replaced by NArAr′). The change is probably initiated by the attraction of the mobile aryl group for the unshared electrons of the nitrogen (process *a*); the electronic displacements *b* and *c* are thereby set up, and finally the aryl group breaks away from the oxygen, processes *a*, *b*, and *c* becoming complete to give the isomeric compound.

The Stevens Rearrangement of Quaternary Ammonium Salts[81]

In 1928 Stevens and his collaborators observed a transformation in which a benzyl group migrates from the nitrogen atom of a quaternary ammonium salt to the adjacent carbon atom. The process occurs in alkaline solution, being promoted by alkali hydroxides or alkoxides. The first example recorded was the following:



$$\left[C_6H_5\cdot CO\cdot CH_2\cdot \underset{\displaystyle CH_2\cdot C_6H_5}{\underset{|}{N}}(CH_3)_2\right]Br + NaOH \longrightarrow C_6H_5\cdot CO\cdot \underset{\displaystyle CH_2\cdot C_6H_5}{\underset{|}{CH}}\cdot N(CH_3)_2 + H_2O + NaBr.$$

The rearrangement may be written in the generalized form

$$R\cdot CH_2\cdot \overset{\oplus}{N}R'(CH_3)_2 \xrightarrow{-H^{\oplus}} R\cdot CHR'\cdot N(CH_3)_2,$$

and it has been observed in quaternary ammonium salts where R = acetyl, benzoyl, substituted benzoyl (electron-attractive substituents *decreasing* its speed), phenyl, or vinyl, and R′ = benzyl, substituted benzyl (electron-attractive substituents now *increasing* its speed), α-phenylethyl, benzhydryl, 9-fluorenyl or phenacyl. The dimethylammonium radical may also be replaced by piperidinium. The change appears to be unimolecular, and, since they failed to detect any exchange of groups between two different quaternary ammonium salts, the authors consider it to be *intra*molecular.

As in the transformations discussed above, the group migrates to an atom which has unshared electrons, and here again it is easy to visualize its attachment by these electrons simultaneously with the release of the pair by which it was linked originally. This leads to a mechanism of the following type, which is the same in its essentials as that suggested by Stevens and co-workers:

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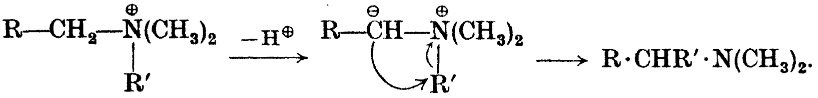
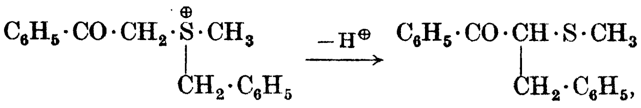
[80] Compare Bennett and Chapman, *Ann. Reports*, 1930, **27**, 121; Chapman and Perrott, *J.C.S.* 1930, 2465.

[81] Stevens *et al.*, *J.C.S.* 1928, 3193; 1930, 2107, 2119; 1932, 55, 1926, 1932.



$$R—CH_2—\overset{\oplus}{N}(CH_3)_2(R') \xrightarrow{-H^{\oplus}} R—\overset{\ominus}{C}H—\overset{\oplus}{N}(CH_3)_2(R') \longrightarrow R\cdot CHR'\cdot N(CH_3)_2.$$

The analogous reaction has been observed in a sulphonium compound,



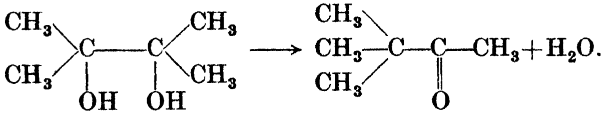
$$C_6H_5\cdot CO\cdot CH_2\cdot\overset{\oplus}{S}(CH_2\cdot C_6H_5)\cdot CH_3 \xrightarrow{-H^{\oplus}} C_6H_5\cdot CO\cdot CH(CH_2\cdot C_6H_5)\cdot S\cdot CH_3,$$

but not in an oxonium compound.[82]

The rearrangements of hydroxysulphones and related compounds, which have been studied by Smiles and his co-workers, may be represented by a similar mechanism.[83]

The Pinacol-Pinacolone and Allied Transformations

The conversion of tetramethylethylene glycol (pinacol) to methyl *tert*-butyl ketone (pinacolone), first observed by Fittig,[84] involves the loss of a molecule of water accompanied by the transference of a methyl group from one carbon atom to the next:



Other tertiary glycols behave similarly. In unsymmetrical compounds the nature of the product (or products) will depend upon the 'orientation' of the elimination of hydrogen and hydroxyl (governed by the relative capacities of the attached groups for electron-release), and also upon the ease with which the different groups can migrate from one carbon to the other.[85] Secondary glycols give aldehydes, as exemplified by the conversion of hydrobenzoin to diphenylacetaldehyde,

$$C_6H_5\cdot CH(OH)\cdot CH(OH)\cdot C_6H_5 \longrightarrow (C_6H_5)_2\cdot CH\cdot CHO+H_2O.$$

If one secondary and one tertiary alcoholic group is present, two types of rearrangement are possible, the semipinacolinic and semihydrobenzoinic changes, which lead respectively to a ketone and an aldehyde, e.g.

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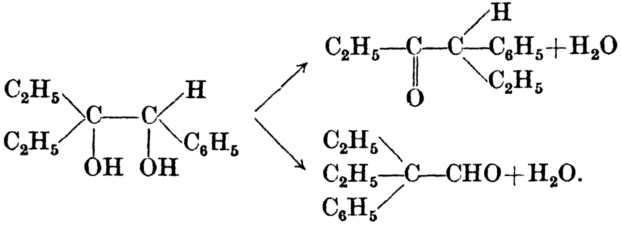
[82] Thomson and Stevens, *J.C.S.* 1932, 69.

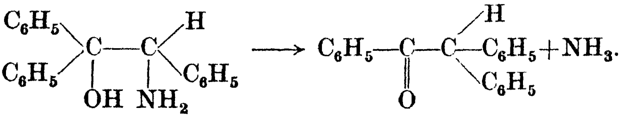
[83] For a summary of this work and references to original literature, see *Ann. Reports*, 1939, **36**, 197.

[84] *Annalen*, 1860, **114**, 56.

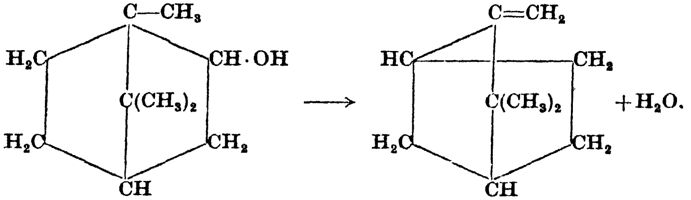
[85] Ingold, *Ann. Reports*, 1928, **25**, 133; Bennett and Chapman, ibid. 1930, **27**, 114; Kon, ibid. 1933, **30**, 181. See also Baker, *Tautomerism*, ch. xiv.



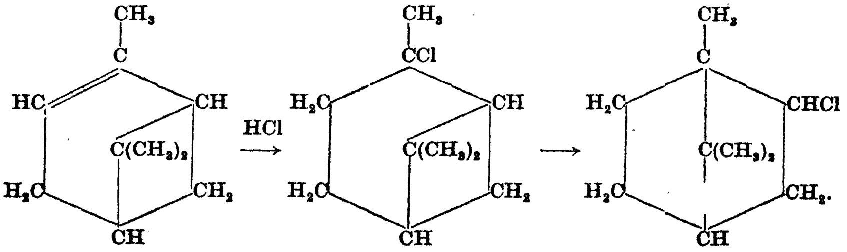
All these transformations occur in the presence of *acids*. A similar migration, with elimination of ammonia, takes place when $\alpha\beta$-aminoalcohols react with nitrous acid (pinacolic deamination),[86] e.g.



The Wagner-Meerwein Rearrangement, which is familiar in terpene chemistry, and which may or may not involve the elimination of water or hydrogen chloride, is essentially a 'pinacolic' change. Well-known examples are the conversion of borneol to camphene (water removed), and of pinene hydrochloride, which is stable only below 0°, to bornyl chloride (no elimination).



(Borneol) (Camphene)



(Pinene) (Pinene hydrochloride) (Bornyl chloride)

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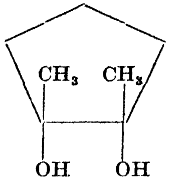
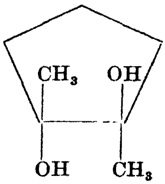
[86] McKenzie *et al.*, *J.C.S.* 1924, **125**, 2105, and later.

The Pinacol and Wagner transformations differ from those dealt with above (Beckmann, Hofmann, etc.) in that the group migrates to an atom which has no unshared electrons, and a migration of an *intra*molecular type is therefore less easy to visualize. Nevertheless, there are indications that the group never becomes free. Thus, when *cis*- and *trans*-1:2-dimethyl*cyclo*pentane-1:2-diols are refluxed with 30 per cent. sulphuric acid, the *cis*-form gives 2:2-dimethyl*cyclo*pentanone in 87 per cent. yield, whereas the *trans*-isomeride produces only brown tars.[87] The two forms may be represented as follows:

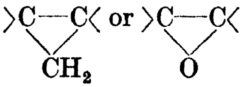


cis.



trans.

and it appears that migration occurs only when the methyl group can displace the hydroxyl by attacking the opposite side of the carbon atom holding it. This difference in behaviour of the geometrical isomerides could not be understood if the methyl group became completely detached from the molecule, and it must be concluded that the change is *intra*molecular; the conclusion refers only to the transference of the alkyl group, however, and in cases where there is no elimination it is quite probable that the halide or other anion dissociates from one point of the molecule and recombines at another (see below).

The earliest mechanisms suggested for the representation of these changes assumed elimination of water with the formation of a *cyclo*propane or ethylene oxide ring,  $\underset{CH_2}{>C{-}C<}$ or $\underset{O}{>C{-}C<}$, which then ruptured to give the product of the change.[88] Such a view is not supported by the experimental evidence, however, and, moreover, is not likely to be applicable to cases where there is no elimination.[89]

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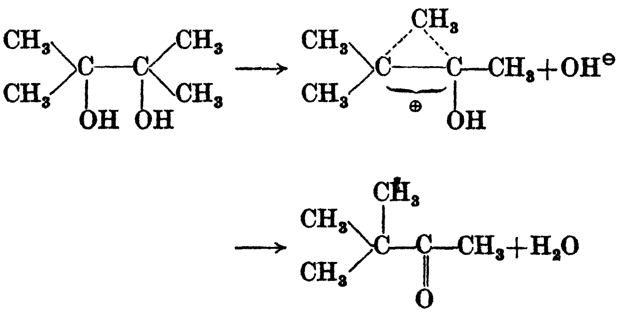
[87] Bartlett and Bavley, *J. Amer. Chem. Soc.* 1938, **60**, 2416.

[88] Erlenmeyer Sr., *Ber.* 1881, **14**, 322; Erlenmeyer Jr., *Annalen*, 1901, **316**, 84; Ruzicka and Liebl, *Helv. Chim. Act.* 1923, **6**, 267.

[89] For a critical discussion of these theories, see Henrich, *Theories of Organic Chemistry*, trans. by Johnson and Hahn (John Wiley & Sons, New York, 1922), p. 530. Also Ingold, *Ann. Reports*, 1924, **21**, 96.

Later suggestions have involved the operation of 'partial valencies',[90] the rearrangement of a molecule having free valencies,[91] or preliminary ionization followed by rearrangement of the cation,[92] and it appears probable that the truth is to be found in a combination of Meerwein's ionization mechanism with Sir Robert Robinson's conception of partial valencies, which may be expressed in terms of the phenomenon of mesomerism.

An electronic representation of the pinacol and Wagner transformations put forward by Ingold in 1928[93] is the same in principle as the general scheme for a number of rearrangements suggested later by Whitmore.[66] It postulates the migration of the alkyl group with its electron pair. This can now be modified by introducing the conception of mesomerism,[94] and the representation thus obtained provides the most satisfactory picture of the mechanism of these changes yet suggested. Adopting Meerwein's view that ionization is the first step, it is supposed that the compound dissociates, giving an anion and a mesomeric cation in which the positive charge is distributed between two carbon atoms (this is the electronic equivalent of the conception of partial valencies). This cation then either loses a proton (if the transformation involves elimination) or adds an anion (if there is no elimination) to form the product. For pinacol and pinene hydrochloride respectively the mechanism may be written as follows:



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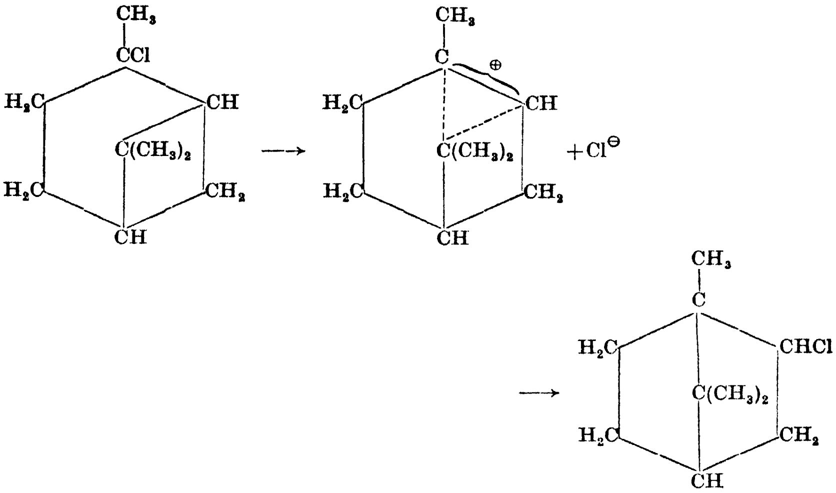
[90] Robinson, *Mem. Manchester Phil. Soc.* 1920, **64**, No. 4.

[91] Tiffeneau, *Compt. rend.* 1906, **143**, 684.

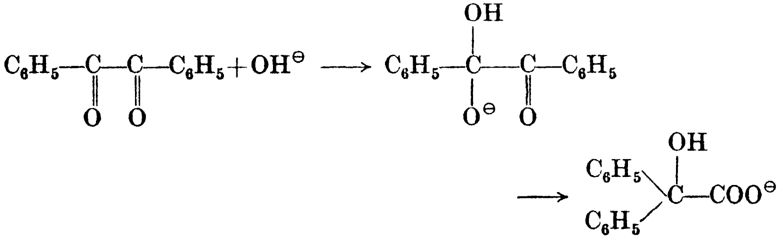
[92] Meerwein and Wortmann, *Annalen*, 1924, **435**, 190.

[93] *Ann. Reports*, 1928, **25**, 133.

[94] Suggested by Professor Ingold in a private communication to the author.



The transformation of benzil to benzilic acid is no doubt of the same type; it occurs in alkaline solution and its speed is proportional to the concentrations of both benzil and hydroxyl ion.[95] This is in harmony with a scheme in which the first step is the addition of hydroxyl ion at carbonyl carbon to give a complex negative ion.[96] An addition compound of benzil and potassium hydroxide has actually been isolated, and it rearranges to give potassium benzilate.[97] The transformation is thus



$$C_6H_5-\underset{\underset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle O}{\|}}{C}-C_6H_5+OH^{\ominus} \longrightarrow C_6H_5-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle O^{\ominus}}{|}}{C}}-\underset{\underset{\displaystyle O}{\|}}{C}-C_6H_5 \longrightarrow \begin{matrix}C_6H_5\\ C_6H_5\end{matrix}\!\!>\overset{\overset{\displaystyle OH}{|}}{C}-COO^{\ominus}$$

but it is difficult to formulate a detailed mechanism.

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[95] Westheimer, *J. Amer. Chem. Soc.* 1936, **58**, 2209.

[96] Robinson, *Ann. Reports*, 1923, **20**, 118; Ingold and Shoppee, *J.C.S.* 1928, 371.

[97] Scheuing, *Ber.* 1923, **56**, 252.

NOTE TO PAGE 185.

The Benzidine Transformation. Since the revision of this chapter and the correction of the proof, the text of Sir Robert Robinson's recent Presidential Address to the Chemical Society has become available. The reader is referred to *J.C.S.* 1941, **220**.

XIV

A REVIEW OF SOME STEREOCHEMICAL PROBLEMS

THE existence of two kinds of quartz crystal, which had opposite effects upon a beam of polarized light, was observed by Biot in 1815; the optical activity was dependent upon the arrangement of the *molecules* in the crystal, and was absent in other forms of silica. Some thirty to forty years later Pasteur discovered *l*-tartaric acid, which differed from the ordinary (*d*-) acid in crystalline form and gave, *when in solution*, an equal and opposite rotation of the plane of polarization. The optical isomerism was here to be ascribed to different spacial configurations of the *atoms* within the molecule, and Pasteur pointed out that the relationship of the *d*- and *l*-acids must be that of object to mirror-image, the optically inactive racemic acid being composed of equal proportions of the active isomerides. He also devised the three well-known methods for the resolution of racemic substances into their optically active forms. Somewhat later (1873) Wislicenus, on the basis of his researches on the lactic acids, also emphasized the necessity for postulating different arrangements of the atoms in space. Then in 1874 van 't Hoff and Le Bel published their theories of stereoisomerism almost simultaneously. They pointed out that all organic compounds which were known to exhibit optical activity in the liquid state or in solution contained at least one carbon atom linked to four different atoms or groups, and they regarded this feature as being responsible for the dissymmetry of the molecule and hence for the existence of two forms which were non-superimposable and related to each other as object to mirror-image. Van 't Hoff supposed the four groups to be situated at the angular points of a tetrahedron with the carbon atom at the centre; this explained the disappearance of the stereoisomerism when two of the groups became identical.

The van 't Hoff-Le Bel theory being accepted, it was a simple matter to predict the number of isomerides which should be formed by a compound containing a given number of 'asymmetric' carbon atoms, and among the most brilliant applications of the theory was Fischer's determination (1894) of the configurations of the sugars, including the sixteen possible hexoses. The further discoveries of mutarotation and of the α- and β-methylglucosides have led to the modern ring formulae. The conception of the tetrahedral carbon atom was also adopted by Baeyer in his Strain Theory (1885) and by Wislicenus in his interpretation of the geometrical isomerism of olefinic compounds (1887).

A new stage was reached when, in 1899, Pope and Peachey discovered an instance of optical activity with nitrogen as the centre of asymmetry, and the classical methods of stereochemistry have led to the recognition of the tetrahedral configuration for a number of elements other than carbon. Such a disposition of valencies appears to be usual, though not invariable, for elements exhibiting a covalence of four or less, while the octahedral configuration first established by Werner in 1911 for certain cobalt complexes is universal, as far as is known, for six-covalent elements.

Perhaps the most striking advance of the present century, however, is the application of physical methods to the elucidation of stereochemical problems; like other branches of theoretical organic chemistry, stereochemistry has profited in no small degree from the development of these new methods of attack. The late Sir William Pope has described the position as follows:[1]

> 'Just as a fresh outburst of expansion followed on the van 't Hoff-Le Bel theory of the asymmetric carbon atom in 1874 and a further era of progress commenced in the early 90's, so we are again witnessing the opening of a new epoch in the evolution of stereochemistry. The classical stereochemistry based on Pasteur's work will continue to expand, but it is becoming merged in a larger stereochemistry which embraces all chemical substances whether optically active or not. The rapid expansion of modern physics during recent years has provided novel and powerful methods for determining the arrangement of the atoms, and indeed of the components of the atoms, in solid, liquid, and even gaseous substances.'

Thus the tetrahedral configuration of the valencies of carbon was confirmed by one of the earliest triumphs of the Bragg X-ray method, viz. the elucidation of the structure of the diamond crystal, and numerous other results have subsequently been obtained by the same procedure. Dipole moments and band spectra have also played their part in the development of this branch of chemistry, and certain stereochemical problems have been attacked by kinetic methods. Meanwhile, the classical methods have yielded valuable results, as instanced by the discovery of optical activity due to restricted rotation, the preparation of optically active allene derivatives, and the resolution of numerous compounds having elements other than carbon as the centre of dissymmetry. Some of these advances will be considered in the sequel.

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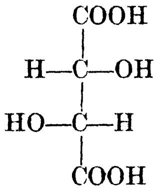
[1] 'Forty Years of Stereochemistry', Messel Memorial Lecture, *J. Soc. Chem. Ind.* **1932, 51,** 229 T.

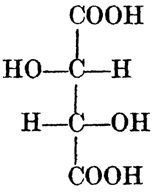
1. *Dissymmetry of Carbon Compounds*

Optical isomerism is possible only if the molecule is dissymmetric in such a way that it is not identical with its mirror-image. It need not, however, be completely devoid of geometrical symmetry; the necessary conditions are fulfilled provided that it has no *plane* or *centre* of symmetry. The absence of an *axis* of symmetry is not necessary.[2] For example, *d*-, *l*-, and *meso*-tartaric acids may be represented by the following projection formulae:



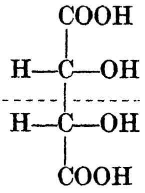
$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{COOH} \end{array}$$

(active)



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{COOH} \end{array}$$

(active)



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{COOH} \end{array}$$

(meso)

and it is evident that the inactive *meso* form has a plane of symmetry (indicated by the dotted line) whereas the active forms have not; they have an axis of symmetry, however.

The actual condition for optical activity is, therefore, the absence of certain elements of symmetry, and not the presence of an 'asymmetric' carbon atom; such an atom provides a special, though admittedly the most common, case of dissymmetry.[3] Van 't Hoff actually predicted the possibility of optical activity in certain cases where there is no 'asymmetric' carbon atom as usually understood. The compounds to which he referred were allene derivatives having the general formula ${}^{a}_{b}\!\!>\!\mathrm{C{=}C{=}C}\!<\!{}^{c}_{d}$. It is universally recognized that groups may rotate freely about a single bond but that such rotation is prevented by a double bond. The olefinic linkages in substituted allenes thus endow the molecule with a certain rigidity, and the tetrahedral disposition of the carbon valencies causes the groups attached to the terminal atoms to lie in different planes (see Fig. 19; this is best understood by the use of a model, however). If now these groups are all different, or even if only those linked to the same carbon are different as in ${}^{a}_{b}\!\!>\!\mathrm{C{=}C{=}C}\!<\!{}^{a}_{b}$, the *molecule as a whole* is dissymmetric; it is non-superimposable upon its mirror image. Up to 1935 all attempts to demonstrate optical activity in allene derivatives were unsuccessful. Similar characters are possessed, however, by compounds in which either one or both double bonds are replaced by rings as in

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[2] Pope, loc. cit., p. 232 T. The terms here employed are defined most simply as follows. A *plane of symmetry* is an imaginary plane dividing the structure into two parts, one of which is the mirror-image of the other. A *centre of symmetry* is a point such that all lines drawn through it meet corresponding points of the structure at equal distances on either side. An *axis of symmetry* is an imaginary line such that, if the structure be rotated about it through 360°, it is coincident with itself at least twice.

[3] The discovery of the heavy isotope of hydrogen (deuterium, D) naturally led to speculations regarding the possibility of optical activity in compounds of the type CHDRR′. Attempts to observe such activity have been unsuccessful, however. See Maitland, *Ann. Reports*, 1939, **36**, 237.

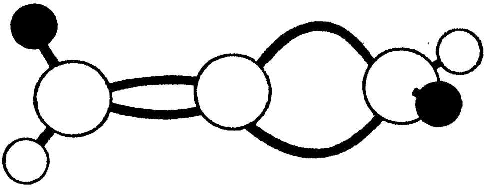
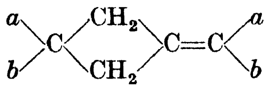
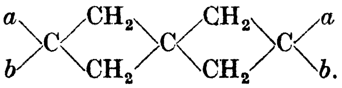


FIG. 19. Diagram of allene derivative:

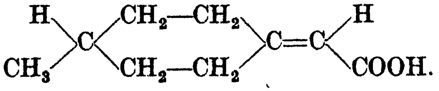
$${}^{a}_{b}\!\!>\!\mathrm{C{=}C{=}C}\!<\!{}^{a}_{b}.$$



or



An instance of optical activity in a compound of the former type was found when Perkin, Pope, and Wallach prepared and resolved 1-methyl*cyclo*hexylidene-4-acetic acid,[4]



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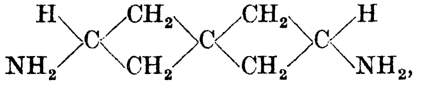
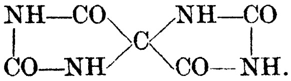
[4] *J.C.S.* 1909, 95, 1789.

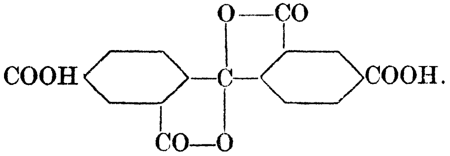
Cases of the latter type were provided later, as exemplified by Janson and Pope's resolution[5] of the diamine



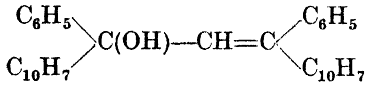
and a modification of this type of stereoisomerism was found when Pope and Whitworth resolved *spiro*-5:5-dihydantoin,[6]



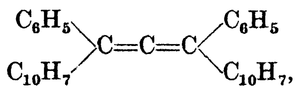
Another example of optical isomerism in the absence of an 'asymmetric' carbon atom had meanwhile been observed by Mills and Nodder[7] who resolved the compound



Then, in 1935, sixty years after van 't Hoff's prediction of the dissymmetry of allene derivatives, the preparation of the optically active forms of one of these compounds was achieved by Maitland and Mills.[8] In the method which ultimately proved successful they employed 'asymmetric catalysis'. The alcohol



was prepared and dehydrated in benzene solution in presence of optically active camphorsulphonic acid; by using the *d*- and *l*-acids in turn the corresponding active forms of diphenyldinaphthylallene,



were obtained.[9] The correctness of van't Hoff's prediction was thus demonstrated. Shortly after the announcement of Maitland and Mills's result, Kohler, Walker, and Tishler reported the resolution, by fractional crystallization of its brucine salts, of a similar compound,[10] viz.

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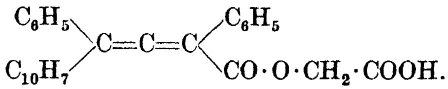
[5] *Chem. and Ind.* 1932, **51**, 316.

[6] *Proc. Roy. Soc.* 1931, **134** A, 357.

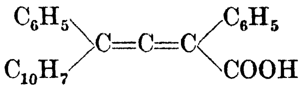
[7] *J.C.S.* 1921, **119**, 2094.

[8] *Nature*, 1935, **135**, 994; *J.C.S.* 1936, 987.

[9] Maitland and Mills suggest the intermediate formation of the alcohol camphorsulphonates. The alcohol (which contains an 'asymmetric' carbon atom) was a mixture of equal parts of *d*- and *l*-forms, and optically active compounds are known to react with such forms at unequal speeds. Other optically active acids may be used instead of camphorsulphonic, but the dehydration process required a much longer time when tartaric or mandelic acid was employed (Clemo, Raper, and Robson, *J.C.S.* 1939, 431). When one α-naphthyl group was replaced by *p*-tolyl, no optical activity was detected.

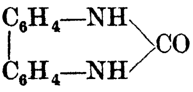


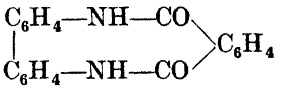
This is actually the carboxymethyl ester of the acid

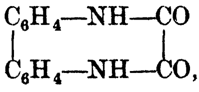


which Lapworth and Wechsler had prepared in 1910, but failed to resolve.[11] The attack on one of the most interesting of the outstanding problems of classical stereochemistry has thus been brought to a successful conclusion.

The optical activity of allene derivatives depends upon the dissymmetry of the molecule as a whole, and not upon the presence of an 'asymmetric' carbon atom; it is made possible by the lack of free rotation about the carbon to carbon double bonds. An analogous case is found in derivatives of diphenyl and certain other compounds, where the rotation about a *single* bond is restricted by the presence of substituents in suitable positions.[12] The reported existence of cyclic derivatives of benzidine (4:4′-diaminodiphenyl[13]), e.g.







had led Kaufler to the conclusion, in 1907, that the amino-groups must be closer together than would be the case if the usually accepted formula (I) for diphenyl were correct.[14] Accordingly, he suggested a folded structure (II) which was later found to provide a possible

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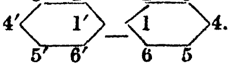
[10] *J. Amer. Chem. Soc.* 1935, **57**, 1743.

[11] *J.C.S.* 1910, **97**, 38.

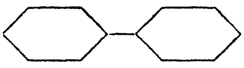
[12] For an excellent summary and full bibliography up to 1932, see Adams and Yuan, *Chem. Reviews*, 1933, **12**, 261.

[13] The positions in diphenyl are numbered as follows: 

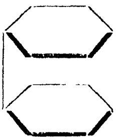
[14] *Annalen*, 1907, **351**, 151; *Ber.* 1907, **40**, 3250. In the representation of the Kaufler structure (II) the rings are perpendicular to the plane of the paper, and the thick lines indicate the near sides.

explanation of supposed cases of stereoisomerism among diphenyl derivatives.[15]

I

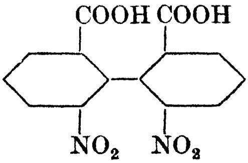


II

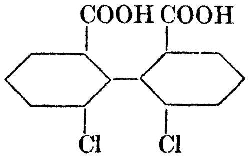


In 1926, however, a systematic re-examination of the subject, principally by Turner and his collaborators, led to the complete collapse of the evidence upon which the Kaufler formula was based.[16] Practically all the relevant experimental observations were proved to be erroneous; in no case were the amino-groups of benzidine combined in a ring, and the reputed stereoisomerides were structurally distinct (e.g. of the two supposed 3:3′-dinitrobenzidines one was actually the 2:3′-dinitro compound). Further, 4:4′-dinitro- and -dichlorodiphenyls were both shown to have zero dipole moment,[17] a result which was possible only if the two nuclei were coaxial. The original formula for diphenyl (I) was thus re-established.

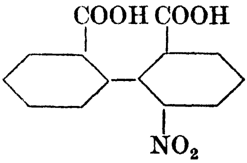
The Kaufler formula being discredited, it was now possible to give a rational interpretation to an observation which had been made originally by Christie and Kenner in 1922.[18] They had succeeded in resolving 6:6′-dinitrodiphenic acid (III) into optically active forms, and by 1926 the resolution of five other substituted diphenyls had been achieved, e.g. IV and V.



III



IV



V

In all these compounds at least three substituents were situated in *ortho*-positions with respect to the junction of the nuclei, and compounds with less than three substituents so placed resisted resolution. Since the nuclei are known to have a common axis, dissymmetry is possible only if they lie in different planes; this was pointed out by Christie and Kenner.[18] Moreover, *both* rings must be substituted unsymmetrically, as demonstrated experimentally by Adams and his co-workers, who have found, for example, that while VI is resolvable VII is not.[19]

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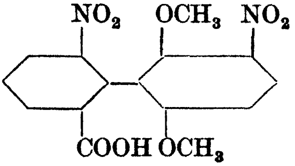
[15] Cain *et al.*, *J.C.S.* 1912, **101**, 2298, and later. Kenner and Stubbings, ibid. 1921, **119**, 593.

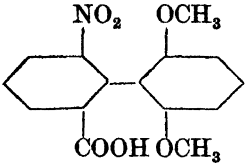
[16] Ibid. 1926, 2476, and other papers 1926–8; Christie and Kenner, ibid. 1926, 470, 671.

[17] Williams and Weissberger, *J. Amer. Chem. Soc.* 1928, **50**, 2332.

[18] *J.C.S.* 1922, **121**, 614.

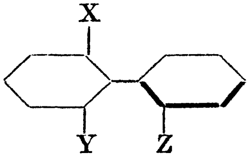


VI

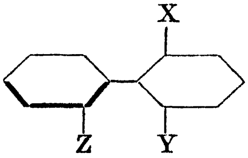


VII

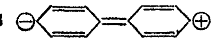
If these conditions are fulfilled, non-superimposable mirror-image forms such as VIII and IX (where the nucleus containing the substituent Z is not in the plane of the paper) can exist.



VIII



IX

If free rotation is possible about the bond joining the nuclei, however, the molecule will be able to take up a uniplanar configuration, and there will be no dissymmetry. According to the modern conception of mesomerism, the freedom of rotation of the nuclei is reduced both in diphenyl itself and in its derivatives by the participation in the mesomeric state of structures such as , for the central bond will have, to some extent, the characters of an olefinic linkage. This will tend, however, to hold the nuclei in one plane.[20] Clearly, dissymmetry will be made possible only by the operation of some factor which maintains a non-coplanar configuration. Such a factor was postulated in 1926 by Turner and Le Fèvre,[21] by Bell and Kenyon,[22] and by Mills.[23] Since optical activity had been observed only when at least three substituents were placed *ortho* to the junction of the nuclei, the dissymmetry was clearly connected with substituents in these positions; it is not to be expected, indeed, that groups otherwise placed could exert the necessary influence.

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[19] See ref. 12, p. 293.

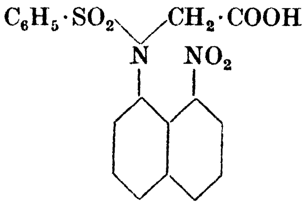
[20] Sutton, *Trans. Faraday Soc.* 1934, **30**, 791.

[21] *Chem. and Ind.* 1926, **45**, 831.

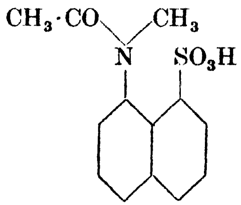
[22] Ibid., p. 864.

[23] Ibid., pp. 883, 905.

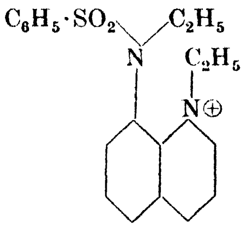
The stereoisomerism of diphenyls is therefore ascribed to the effect of *ortho*-substituents in preventing the nuclei from becoming coplanar; their rotation is restricted in such a way as to render this particular configuration impossible. In confirmation of this view, Mills and his collaborators have observed similar phenomena in quite different systems;[24] they have resolved *peri*-naphthalene derivatives such as X and X*a*, the quinolinium ion X*b*, and finally the benzene derivatives XI and XI*a*.



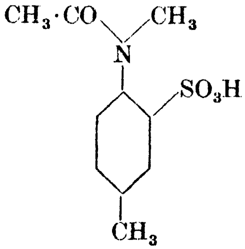
X



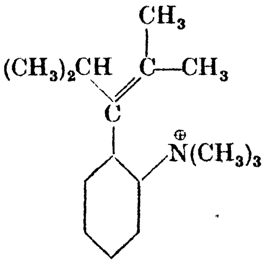
X*a*



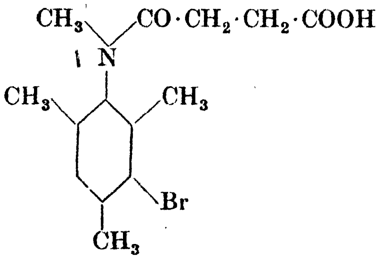
X*b*



XI



XI*a*



XI*b*

The un-nitrated analogue of X, the tertiary base corresponding to X*b*, the acid having —COOH in place of —SO_3H in XI, and the analogue of XI *a*, in which $(CH_3)_2CH{-}\underset{|}{C}{=}C(CH_3)_2$ is replaced by $CH_3\cdot CH_2{-}\underset{|}{C}{=}CH\cdot CH_3$ are not resolvable, and the optical activity must depend upon the restriction of the rotation of the disubstituted amino-group —NRR′ (or substituted vinyl in XI *a*) about the bond linking it to the nucleus. Adams and his co-workers have also resolved the compound XI *b*, and certain suitably substituted heterocyclic nitrogen compounds.[25] The observations made in the diphenyl series are not, therefore, peculiar to this system, and hence require for their interpretation a theory, such as that outlined above, which is applicable in any system where the groups are suitably placed.

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[24] *J.C.S.* 1928, 1291; 1932, 2209; 1937, 274; 1939, 460.

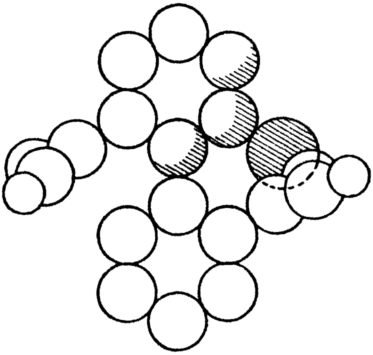

FIG. 20. 6-Chlorodiphenic acid. (Reproduced from Mills, *Chem. and Ind.* 1926, **45**, 883.)

The manner in which groups give rise to this effect is not, as yet, perfectly clear, since their influence might arise from their polar characters or from their volumes. Mills has suggested that a sufficient interpretation is provided by postulating mere mechanical obstruction, dependent solely upon the bulk of the groups, and models constructed to scale show that groups can interfere in this way and prevent the nuclei from becoming coplanar. This is obvious from Fig. 20 (reproduced from Mills's original contribution in *Chemistry and Industry*), which represents 6-chlorodiphenic acid; the carboxyl attached to the lower nucleus cannot pass either the chlorine (large shaded circle) or the carboxyl linked to the upper ring, and hence the nuclei can rotate only through a small arc *which does not include the uniplanar position*. Evidence obtained subsequently by Adams, Turner, and their collaborators is in harmony with this Obstacle

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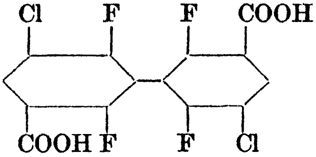
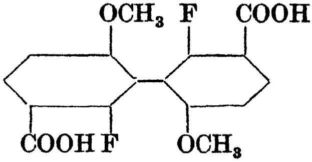
[25] See ref. 12, p. 317, and *J. Amer. Chem. Soc.* 1940, **62**, 2191.

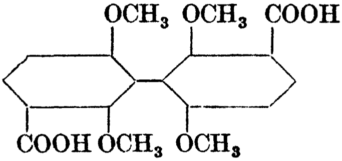
Theory of Mills.[26] Thus, certain diphenyls having *four* substituents in *ortho*-positions are not resolvable, e.g. XII, XIII, and XIV.



XII

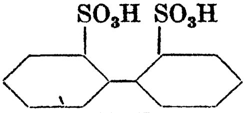


XIII

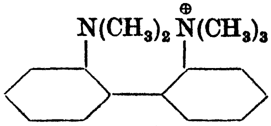


XIV

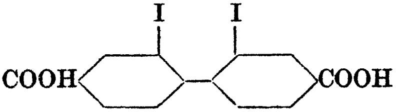
Apparently the fluorine and methoxyl substituents (both of which have small diameters) are not sufficiently large to interfere with the rotation of the nuclei. Then, there is a steady gradation in the ease with which substituted diphenyls pass into their inactive forms, and the observed sequence agrees quite well with the order of sizes of the groups; for example, when two *o*-substituents in one ring remain constant and one group is introduced into an *o*-position in the other ring, the order of effectiveness in stabilizing the active form is Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F. The effect of bulk is emphasized by the demonstration that, when the groups are sufficiently large to collide with the hydrogen of the other ring, *two o*-substituents can give rise to optical activity as in XV, XVI, XVII, and XVIII.



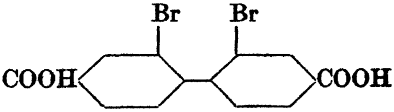
XV[27]



XVI[28]



XVII[29]



XVIII[30]

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[26] See ref. 12, pp. 296 ff.

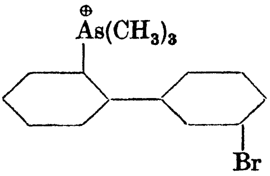
[27] Lesslie and Turner, *J.C.S.* 1932, 2394.

[28] Shaw and Turner, ibid. 1933, 135.

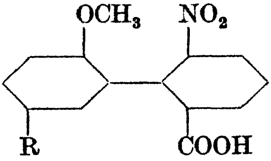
[29] Searle and Adams, *J. Amer. Chem. Soc.* 1933, 55, 1649.

[30] Idem, ibid. 1934, 56, 2112.

Finally, Lesslie and Turner have been able to realize optical activity in a diphenyl derivative containing only *one* *o*-substituent;[31] this was achieved by the preparation and resolution of the ion XIX. The $\overset{\oplus}{As}(CH_3)_3$ group appears therefore to be sufficiently bulky to cause restriction of rotation when both *o*-positions of the other nucleus are occupied by hydrogen.



XIX



XX

Notwithstanding all this evidence of the importance of the sizes of the *o*-substituents, however, the stereoisomerism is influenced, to some extent at least, by other factors. Thus, Adams and co-workers have observed a definite influence of groups in positions other than those *ortho* to the junction of the nuclei; in a series of compounds of the general formula XX the stability of the active form was dependent upon the nature of R.[32] The position of R is also a factor determining the stability.[33] While, therefore, the experimental evidence leads to the conclusion that the *bulk* of the substituents in *o*-positions is mainly responsible for the optical activity of diphenyl derivatives, the intervention of other factors cannot be entirely neglected.

2. *The Configurations of Geometrical Isomerides*

As a result of the absence of free rotation about an olefinic linkage, the groups attached to a pair of doubly bound carbon atoms occupy fixed positions relatively to one another. The presence of four different groups does not lead to optical activity, however, and this is in harmony with van 't Hoff's tetrahedral theory, according to which the groups lie in one plane and do not therefore give rise to molecular dissymmetry. But in cases where the groups attached to each carbon atom are different, *cis* and *trans* isomerides (geometrical isomerides) exist, having the relationship represented, in accordance with the views of Wislicenus (1887), as follows:

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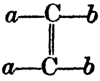
[31] *J.C.S.* 1933, 1588.

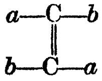
[32] *J. Amer. Chem. Soc.* 1932, 54, 4434.

[33] Ibid. 1934, 56, 1787; 1935, 57, 1592; 1938, 60, 1411.



$$\begin{array}{c} a\text{—}C\text{—}b \\ \| \\ a\text{—}C\text{—}b \end{array}$$

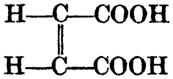
cis



$$\begin{array}{c} a\text{—}C\text{—}b \\ \| \\ b\text{—}C\text{—}a \end{array}$$

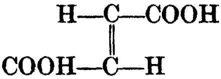
trans

The most widely studied example is, of course, that of maleic and fumaric acids (hence the terms maleinoid and fumaroid). Their preparation from malic acid, and the products of reduction, oxidation, and addition indicate the same structural formula for each, viz. COOH—CH=CH—COOH. They are optically inactive, and they differ in solubility, melting-point, and other properties which are identical in *d* and *l* optical isomerides. Their formulae are written



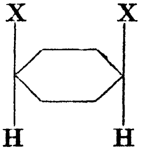
$$\begin{array}{c} \mathrm{H\text{—}C\text{—}COOH} \\ \| \\ \mathrm{H\text{—}C\text{—}COOH} \end{array}$$

and

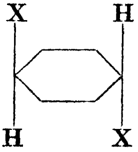


$$\begin{array}{c} \mathrm{H\text{—}C\text{—}COOH} \\ \| \\ \mathrm{COOH\text{—}C\text{—}H} \end{array}$$

Geometrical isomerism is also observed in a large number of cyclic compounds where the ring confers the necessary rigidity upon the molecule, e.g. the hexahydroterephthalic acids

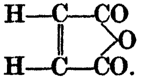


and



(the ring is here to be visualized as in a plane at right angles to the paper). Certain of these cyclic compounds are dissymmetric structures, and some have been resolved.

In the case of maleic and fumaric acids the former is given the *cis* configuration on account of its ability to form an anhydride



Wislicenus attempted to devise other methods for the determination of the configurations of geometrical isomerides. These were based upon the expectation of *cis* addition and elimination of groups, but Michael[34] has shown that they are of no value. Thus, acetylene dicarboxylic acid which, according to the views of Wislicenus, should add bromine to give dibromomaleic acid,

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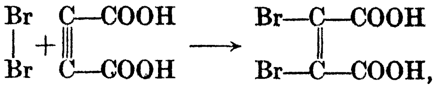
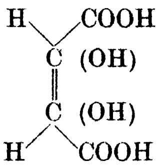
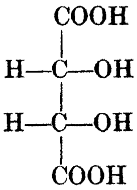
[34] *J. pr. Chem.* 1892, **46**, 210; 1895, **52**, 307.



actually gives dibromofumaric in major quantity, and halogen acid is eliminated far more easily from chloro- and bromo-fumaric acids than from their *cis*-isomerides. The production of *meso*tartaric and racemic acids by oxidation of maleic and fumaric acids respectively is in harmony with the postulate of *cis*-addition, e.g.





but bromine gives the reverse (*trans* addition). A survey of available data, indeed, leads to the conclusion that *trans* addition or elimination is the rule and not the exception.[35] The formation or fission of cyclic structures provides the only chemical method by which the configurations of geometrical isomerides can be determined with any degree of certainty. In some cases information has been obtained by the application of physical methods. Thus for a *s*-dihalogenoethylene the *cis* form should have a considerable dipole moment while the *trans* form should be non-polar, and the experiments of Errera have actually given results in accordance with this view.[36] The distances between the chlorine atoms in *cis* and *trans* dichloroethylenes provide similar evidence.[37]

Comparable with the stereoisomerism of ethylene derivatives is that of compounds containing the C=N or N=N linking. The existence of isomerism among unsymmetrical oximes (e.g. three benzildioximes, two benzilmonoximes,[38] two oximes of benzaldehyde[39]) was given a satisfactory interpretation by Hantzsch and Werner, who supposed that the three valencies of nitrogen were not in the same plane, and that the compounds were geometrical isomerides,[40] e.g.

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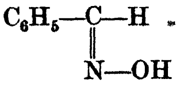
[35] See Frankland, *J.C.S.* 1912, **101**, 673.

[36] *Compt. rend.* 1926, **182**, 1623.

[37] Debye, *Physikal. Z.* 1930, **31**, 419.

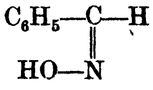
[38] V. Meyer and Auwers, *Ber.* 1888, **21**, 784, 3510; 1889, **22**, 705.

[39] Beckmann, ibid. 1889, **22**, 429, 1631.



$$\begin{array}{c} C_6H_5\text{—}C\text{—}H \\ \| \\ N\text{—}OH \end{array}$$

syn

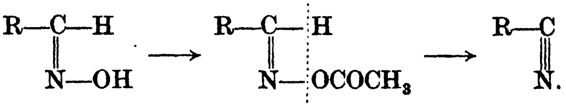


$$\begin{array}{c} C_6H_5\text{—}C\text{—}H \\ \| \\ HO\text{—}N \end{array}$$

anti

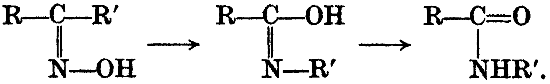
The isomerides differ in much the same way as do *cis* and *trans* ethylene derivatives, and only the stereochemical interpretation can account for the absence of isomerism in symmetrical oximes ($CRR{=}NOH$ where R groups are identical) and for certain instances of optical activity which have been observed.[41] The same view is applicable to the isomerism of hydrazones and related compounds, and of the diazotates,[42] and although criticized adversely at times[43] it has received general acceptance.

Hantzsch's methods of determining the configurations of isomeric oximes resembled those which Wislicenus attempted to apply to the analogous olefinic compounds; they depended upon the assumption of *cis* interaction.[44] In the case of the aldoximes *one* isomeride readily gives a nitrile on acetylation and subsequent removal of acetic acid by alkali, and this was assumed to have the *syn* configuration (H and OH adjacent), i.e.



$$\begin{array}{c} R\text{—}C\text{—}H \\ \| \\ N\text{—}OH \end{array} \longrightarrow \begin{array}{c} R\text{—}C\text{—}\vdots H \\ \| \\ N\text{—}\vdots OCOCH_3 \end{array} \longrightarrow \begin{array}{c} R\text{—}C \\ \| \! \| \\ N. \end{array}$$

The ketoximes were distinguished by the products of the Beckmann Transformation,[45] a *cis* interchange of groups being postulated, i.e.



$$\begin{array}{c} R\text{—}C\text{—}R' \\ \| \\ N\text{—}OH \end{array} \longrightarrow \begin{array}{c} R\text{—}C\text{—}OH \\ \| \\ N\text{—}R' \end{array} \longrightarrow \begin{array}{c} R\text{—}C{=}O \\ | \\ NHR'. \end{array}$$

The theory of preferential *cis* interaction was rendered doubtful by the discovery of *trans* addition and elimination in olefinic compounds (see above), but nevertheless the configurations assigned by Hantzsch to the oximes were not seriously challenged for thirty years. Then, in 1921, Meisenheimer prepared and decomposed the ozonide of triphenylisoxazole and obtained the benzoyl derivative of a benzil monoxime which on hydrolysis yielded the oxime.[46] It was necessary to suppose that these changes occurred as follows:

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[40] *Ber.* 1890, **23**, 11. The earlier view of Meyer and Auwers, which postulated lack of rotation about a carbon to carbon single linkage, proved untenable.

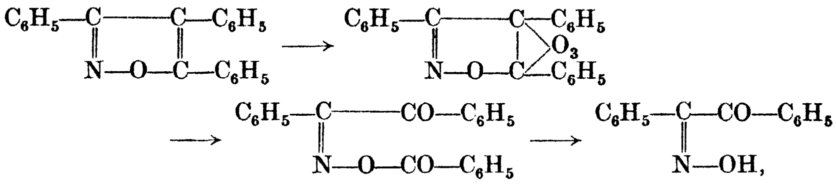
[41] Mills *et al.*, *J.C.S.* 1910, **97**, 1866; 1923, **123**, 312.

[42] Hantzsch, *Ber.* 1894, **27**, 1702. See Cain, *The Chemistry of the Diazo-compounds*, Second Edition (Edward Arnold & Co., 1920).

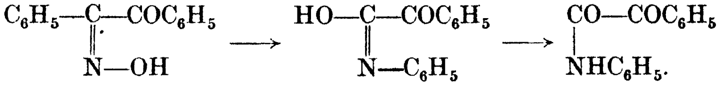
[43] e.g. Atack, *J.C.S.* 1921, **119**, 1175.

[44] *Ber.* 1891, **24**, 13.

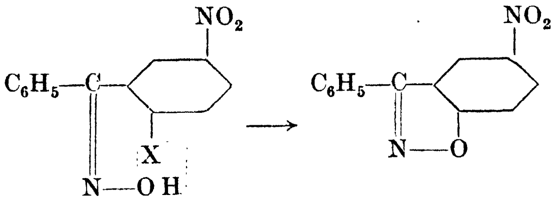
[45] See Chap. XIII.



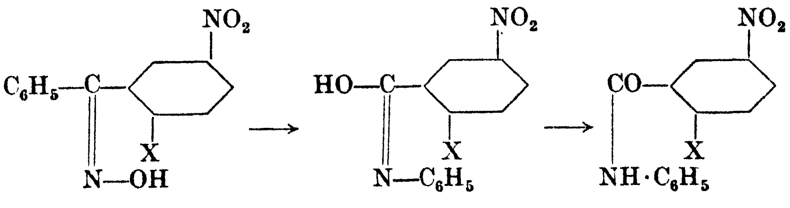
and the configuration of the benzil monoxime was thus determined by a ring-fission method. The Beckmann Transformation of the same oxime, however, gave benzoylformanilide which could be produced only by a *trans* interchange,



Processes of ring formation led to a similar conclusion. For example, one of the isomeric 2-halogeno-5-nitrobenzophenoneoximes, on treatment with alkali, readily eliminated halogen acid forming an isoxazole ring; the proximity of the halogen-substituted nucleus to the hydroxyl group was thus indicated:



The Beckmann Transformation, however, gave the following:



Trans interchange had again occurred, and these and similar results provided a strong argument for the inversion of the Hantzsch configurations of ketoximes.[47] Moreover, Meisenheimer's revised configurations for the benzil monoximes were confirmed by their properties, which indicated a hydrogen bond in the isomeride where the hydroxyl was nearer to carbonyl oxygen,[48] i.e.

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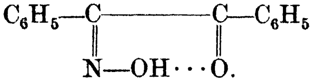
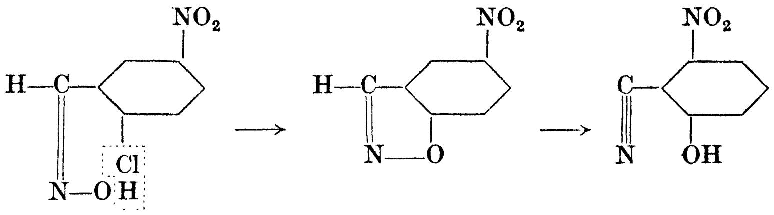
[46] *Ber.* 1921, **54**, 3206.



$$\begin{array}{l} C_6H_5\text{—}C\text{————}C\text{—}C_6H_5 \\ \quad\quad\ \ \| \quad\quad\quad\ \ \| \\ \quad\quad\ N\text{—}OH\cdots O. \end{array}$$

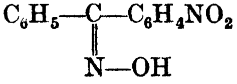
Meanwhile, the necessity for a similar inversion of aldoxime configurations was suggested by Beckmann[49] and by Auwers,[50] and rendered highly probable by the observations of Brady and Bishop.[51] These workers prepared two isomeric 2-chloro-5-nitrobenzaldoximes, and found that one of these gave ring closure with ease:



This was therefore the *anti*-aldoxime. It was, however, the isomeride which Hantzsch, on the basis of ready elimination of acetic acid from its acetyl derivative, would have designated the *syn* compound. The conclusion was therefore drawn that *trans* interaction occurs in the aldoximes, and that here also the formulae arrived at by the Hantzsch method must be inverted.[52]

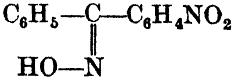
Confirmation of this view has been obtained by Taylor and Sutton[53] from measurements of the dipole moments of oxime-ethers (the oximes themselves were unsuitable for examination owing to association). The two oximes of *p*-nitrobenzophenone having the formulae I and II give the *N*-ethers I*a* and II*a*.

I



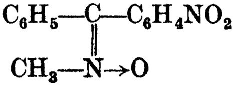
$$\begin{array}{l} C_6H_5\text{—}C\text{—}C_6H_4NO_2 \\ \quad\quad\ \ \| \\ \quad\quad\ N\text{—}OH \end{array}$$

II



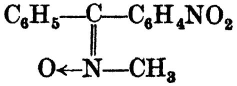
$$\begin{array}{l} C_6H_5\text{—}C\text{—}C_6H_4NO_2 \\ \quad\quad\ \ \| \\ HO\text{—}N \end{array}$$

I*a*



$$\begin{array}{l} C_6H_5\text{—}C\text{—}C_6H_4NO_2 \\ \quad\quad\ \ \| \\ CH_3\text{—}N\rightarrow O \end{array}$$

II*a*



$$\begin{array}{l} C_6H_5\text{—}C\text{—}C_6H_4NO_2 \\ \quad\quad\ \ \| \\ O\leftarrow N\text{—}CH_3 \end{array}$$

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[47] Meisenheimer *et al.*, *Ber.* 1924, **57**, 289; *Annalen*, 1926, **446**, 205.

[48] Taylor and Ewbank, *J.C.S.* 1926, 2818. See Chap. I, p. 22, on the hydrogen bond.

[49] *Ber.* 1923, **56**, 341.

[50] Ibid. 1924, **57**, 446.

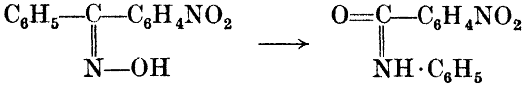
[51] *J.C.S.* 1925, **127**, 1357.

[52] See also Brady, ibid. 1931, 105.

[53] Ibid. 1931, 2190; 1933, 63.

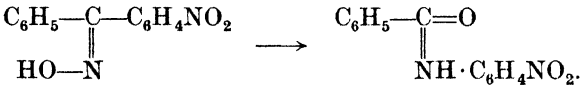
Two dipolar groups, $\overset{\oplus}{N}\left\langle{}^{O}_{O}\right\}^{\ominus}$ and $\overset{\oplus}{N}—\overset{\ominus}{O}$, are present in each, and these groups no doubt give rise to moments of about the same magnitude. In I*a* the moments will co-operate to give a large resultant value, while in II*a* they are in opposite directions and will oppose each other. The experimentally determined moments of the isomeric ethers were 6·60 and 1·09, and definite evidence of the structures of the ethers and hence of the corresponding oximes was thus found. The products of the Beckmann Transformation of the same oximes are as follows:

I.



$$C_6H_5—\underset{\underset{N—OH}{\|}}{C}—C_6H_4NO_2 \longrightarrow O{=}\underset{\underset{NH\cdot C_6H_5}{|}}{C}—C_6H_4NO_2$$

II.

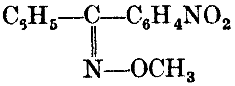


$$C_6H_5—\underset{\underset{HO—N}{\|}}{C}—C_6H_4NO_2 \longrightarrow C_6H_5—\underset{\underset{NH\cdot C_6H_4NO_2.}{|}}{C}{=}O$$

Trans exchange of groups therefore occurs.

For aldoximes, where isomeric *N*-ethers have not been obtained, evidence was forthcoming from a comparison of the dipole moments of *O*-ethers with those of the corresponding ethers of ketoximes. The *O*-methyl ethers of *p*-nitrobenzophenoneoxime and their dipole moments are as follows (I*b* and II*b*):

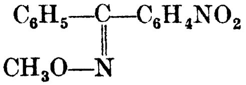
I*b*



$$C_6H_5—\underset{\underset{N—OCH_3}{\|}}{C}—C_6H_4NO_2$$

$\mu = 3{\cdot}75$

II*b*

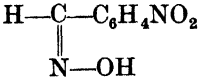


$$C_6H_5—\underset{\underset{CH_3O—N}{\|}}{C}—C_6H_4NO_2$$

$\mu = 4{\cdot}25$

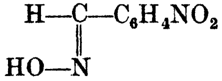
The corresponding *p*-nitrobenzaldoximes and their *O*-ethers are represented by the formulae III, IV, III*b*, and IV*b*:

III (*anti*)



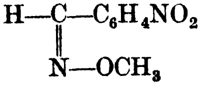
$$H—\underset{\underset{N—OH}{\|}}{C}—C_6H_4NO_2$$

IV (*syn*)



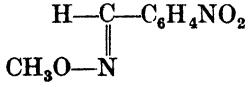
$$H—\underset{\underset{HO—N}{\|}}{C}—C_6H_4NO_2$$

III*b*



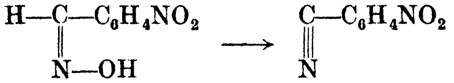
$$H—\underset{\underset{N—OCH_3}{\|}}{C}—C_6H_4NO_2$$

IV*b*



$$H—\underset{\underset{CH_3O—N}{\|}}{C}—C_6H_4NO_2$$

The dipole moments found for these ethers were 3·4 and 3·9 respectively, and by analogy with the ketoxime derivatives (I*b* and II*b*) the aldoxime giving the *O*-ether of larger moment was assigned the *syn* configuration IV. The isomeric (*anti*) aldoxime, however, is the one easily converted to a nitrile, and this reaction therefore occurs as follows:

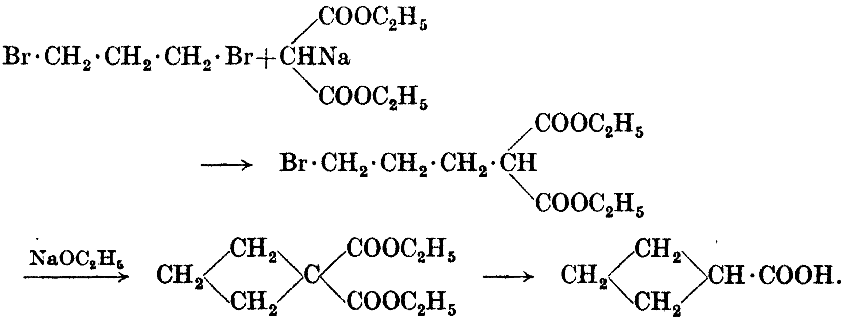


$$\mathrm{H{-}C(=N{-}OH){-}C_6H_4NO_2} \longrightarrow \mathrm{N{\equiv}C{-}C_6H_4NO_2}$$

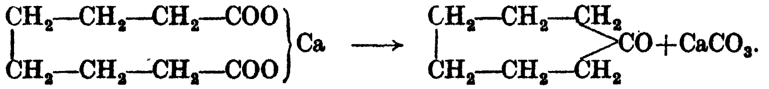
Trans elimination was thus demonstrated again, and the evidence in favour of the inversion of the Hantzsch configurations, both for ketoximes and for aldoximes, seems to be overwhelming.

3. *Formation and Stability of Rings*

An exceedingly clear and interesting account of the early investigations leading to the synthesis of carbon rings having less than six atoms is to be found in the late Professor W. H. Perkin's Pedler Lecture of 1929.[54] Prior to 1883 only the six-membered rings of benzene and *cyclo*hexane were known,[55] but in that year Perkin succeeded in preparing *cyclo*butane carboxylic acid (four-membered ring) by the following series of reactions:



This work was followed by the synthesis (also by Perkin) of *cyclo*propane and *cyclo*pentane derivatives with their three- and five-membered carbon rings. Subsequently, rings of seven and eight carbon atoms were obtained, as, for example, in the synthesis of *cyclo*heptanone or *cyclo*octanone by heating the calcium salts of the appropriate $\alpha\omega$-dicarboxylic acids, e.g.



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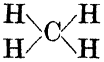
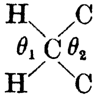
[54] *J.C.S.* 1929, 1347.

[55] Impure specimens of *cyclo*propane and of *cyclo*butane-1:3-dicarboxylic acid had actually been prepared, but not recognized, some one or two years earlier; see ref. 54.

From 1926 onwards, Ruzicka and his collaborators have made a striking advance in the chemistry of carbocyclic compounds by the preparation of ketones and hydrocarbons having rings of carbon atoms up to 34 in number.[56] Finding that a 25 per cent. yield of *cyclo*octanone could be obtained by heating thorium azelate, whereas the calcium salt gave only 5 per cent., they heated the thorium and yttrium salts of the longer chain $\alpha\omega$-dicarboxylic acids, and thus succeeded in synthesizing ketones with rings containing from 9 to 34 carbon atoms, with the exception of those of 25, 27, 31, and 33 members. In most cases reduction by the Clemmensen method gave the corresponding *cyclo*paraffins. When once formed these rings were found to be exceedingly stable, and in fact rings of 15 and 17 carbon atoms are now known to occur naturally in the animal products muscone and civetone.

The Strain Theory. According to the famous Strain Theory of Baeyer, put forward in 1885 and based upon the van 't Hoff tetrahedral model,[57] rings of five and six carbon atoms should be more stable than those having a larger or smaller number. If the valencies of carbon are directed towards the angular points of a *regular* tetrahedron, they will make angles of 109° 28′ with one another (the 'tetrahedral angle'), and Baeyer considered that any distortion of these directions owing to the inclusion of the atoms in a ring would lead to a condition of strain and therefore to decreased stability. This was regarded as being manifested both in the difficulty with which the ring was formed and in the ease with which it was ruptured. Since the distortion is least in five- and six-membered rings, these should constitute the most stable carbocyclic systems. The theory received strong confirmation when, only four months after its publication, Perkin reported the great stability of the *cyclo*pentane ring.[58] Since a large number of other atoms are now known to have tetrahedrally directed valencies, the extension of Baeyer's theory to include the ready formation of compounds such as succinic and glutaric anhydrides and the γ- and δ-lactones is obvious. The peculiar stability of the aromatic nucleus is, of course, ascribed to other causes.

In actual fact, van 't Hoff did not postulate a *regular* tetrahedron except in cases where the four groups linked to the carbon atom are identical,[59] and the inequality of the valence angles in other compounds has been emphasized by Thorpe and Ingold in their 'Valency Deflexion Hypothesis'. Ingold[60] quotes various instances of the inadequacy of the simple Baeyer theory to account for the relative stabilities of ring systems, e.g. the heats of formation of *cyclo*paraffin derivatives which indicate a minimum of stability at *cyclo*butane, the difficulty frequently experienced in the synthesis of the four-membered as compared with the three-membered carbon ring, and the retardation of the hydrolysis of glutaric anhydride by alkyl substituents. It is concluded that the Baeyer theory must be modified in accordance with the probability that the 'tetrahedral angle' of 109° 28′ is found only when the carbon atom is linked to groups of equal size. Thus in  the valence angles will be 109° 28′, but in  θ_1 will be less and θ_2 greater than this, on account of the larger volume of the carbon atoms than of the hydrogen atoms. Thorpe and Ingold do not claim that the chemical characters of a compound are related in any *quantitative* manner with the valence angles calculated on the basis of the molecular volumes of the attached groups; the hypothesis is essentially of a *qualitative nature*,[61] and as such is supported by a considerable number of experimental observations.[62] Thus in the substituted glutaric acid systems

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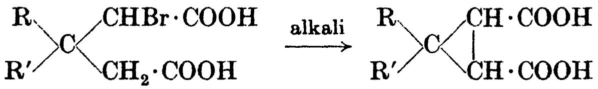
[56] For summaries of this work and full references to original papers see *Ann. Reports*, 1926, **23**, 112; 1928, **25**, 111; 1930, **27**, 151; 1934, **31**, 146. Also Ruzicka, *Chem. and Ind.* 1935, **54**, 2.

[57] *Ber.* 1885, **18**, 2278.

[58] Ibid., p. 3246.



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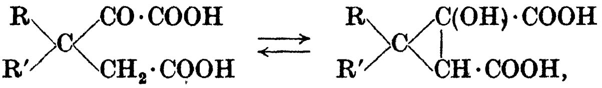

when the groups R and R′ are varied, the facility of *cyclo*propane ring formation is in the order predicted by the hypothesis, e.g. $(C_2H_5)_2 > (CH_3)_2 > (CH_3)H > H_2$; the values of the primary and secondary dissociation constants of β-alkylglutaric acids are also in agreement.[63]

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[59] The reader is referred to a passage quoted by Sidgwick in *The Covalent Link in Chemistry* (Cornell University Press), p. 201.

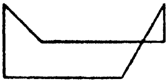
[60] *J.C.S.* 1921, **119**, 305.

[61] Ingold and Thorpe, ibid. 1928, 1318.

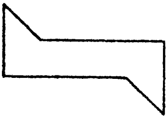
[62] Papers by Thorpe, Ingold, *et al.*, ibid. 1921 onwards.

Similar variations in valency angles are indicated by dipole moments and other physical data. Thus the angle between the oxygen valencies in water, deduced from spectroscopic measurements, is about 105°, whereas the value is appreciably greater in dimethyl ether and greater still in diphenyl ether.[64] It is clear, moreover, that polar influences will operate in many cases as well as bulk effects,[65] and the Baeyer Theory of Strain must be regarded as no more than a rough approximation. It is nevertheless a useful guide provided that its limitations are recognized.

The Sachse-Mohr Theory of Strainless Rings. The stability of Ruzicka's large carbon rings is obviously incapable of interpretation on any hypothesis which regards the atoms as lying in one plane, an assumption which is made, of course, both in the original theory of Baeyer and in its modified form as elaborated by Thorpe and Ingold. As early as 1890, however, Sachse pointed out that in a ring of more than five atoms, where the strain is outward (i.e. the angles between the valencies are larger than the natural tetrahedral angle), a complete release of strain may be brought about by the buckling of the ends.[66] The smallest ring in which this can occur is that of *cyclo*hexane, where there are two possible strainless forms; these are generally referred to as the 'boat' and 'chair' structures, and they may be represented



and



There is no definite evidence that derivatives of *cyclo*hexane exhibit the isomerism which such a theory predicts although Vogel has recently claimed to have isolated two methyl*cyclo*hexanes.[67] Moreover, the properties of glutaric acid derivatives in which two valencies of the β-carbon atom are enclosed in a *cyclo*hexane ring appear, for the most part, to be in harmony with the view that this ring is a plane hexagon with strain.[68] The apparently strained character of the *cyclo*hexane ring may be due to oscillation between the strainless (multiplanar) forms,[69] since there is definite evidence that, given conditions under which such oscillation is impossible, the isomerism predicted by the Sachse theory does actually exist. As a deduction from this theory, Mohr pointed out that the fusion of two buckled *cyclo*hexane rings to give decahydronaphthalene could take place in two ways,[70] as follows:

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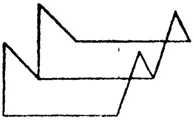
[63] Spiers and Thorpe, ibid. 1925, **127**, 538.

[64] See Glasstone, *Ann. Reports*, 1935, **32**, 126.

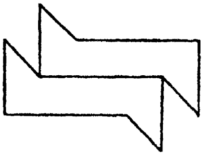
[65] Compare Gane and Ingold, *J.C.S.* 1929, 1691.

[66] *Ber.* 1890, **23**, 1363.

[67] *J.C.S.* 1938, 1323; 1939, 1862.



and



Here again, therefore, two stereoisomerides are predicted, and in this case their isolation has been achieved. The first step was the preparation of two hexahydrohomophthalic anhydrides by Hückel, who followed up this success by isolating, from the two known decahydro-β-naphthols, two different ketones and two decahydronaphthalenes.[71] Other similar pairs of stereoisomerides are known, as, for example, the isomeric cholane derivatives dihydrocholesterol and coprosterol. Rao has shown further that the effect of the decahydronaphthalene system when linked to the β-carbon atom of glutaric acid indicates that it is strainless.[72] There is little doubt, therefore, that the *cyclo*hexane ring, when locked by the junction of another ring at *ortho*-positions, is multiplanar and strainless, and the application of the Sachse-Mohr theory accounts for the stability of the large carbon rings prepared by Ruzicka; the strain is released by their multiplanar configurations.

The ease with which these rings are formed is not dependent upon their stability ('strain factor') alone, however. In spite of their 'strainless' character they are synthesized with difficulty and in small yields, and Ruzicka ascribes this to a 'distance factor', i.e. the distance in the original straight chain compound between the atoms which are linked to form the ring. This is illustrated in Fig. 21, where *a* represents the distance factor which would result in a steadily decreasing yield as the number of carbon atoms increases, and *b* represents the strain factor which would lead to an increasing yield up to five atoms, and thereafter remain constant since the larger rings are strainless. The combination of *a* and *b* gives a curve such as *c*, which indicates the relative yields actually obtained under similar conditions.

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[68] Thorpe *et al.* The evidence is summarized in the late Sir J. F. Thorpe's Presidential Address to the Chemical Society, *J.C.S.* 1931, 1020. See also, however, Desai, ibid. 1932, 1047; Ives, Linstead, and Riley, ibid., p. 1093.

[69] Baker and Ingold, ibid. 1923, **123**, 122; 1925, **127**, 1678.

[70] *J. pr. Chem.* 1918, **98**, 315.

[71] See *Ann. Reports*, 1924, **21**, 92.

[72] *J.C.S.* 1930, 1162. Compare Kandiah, ibid. 1931, 922.

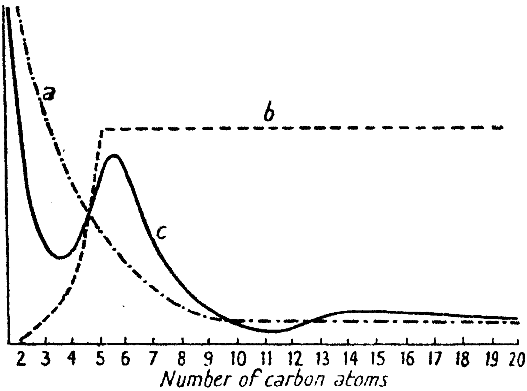
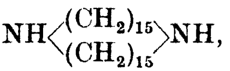


FIG. 21. Factors influencing ring-formation.
(Reproduced from Ruzicka, *Chem. and Ind.* 1935, **54**, 6.)

Large rings containing nitrogen or oxygen in addition to carbon have recently been prepared,[73] e.g.  $NH\begin{matrix}(CH_2)_{15}\\(CH_2)_{15}\end{matrix}NH$, and no doubt their stability is due to a multiplanar configuration. The phthalocyanines, recently discovered by Linstead and his collaborators,[74] with rings of eight carbon and eight nitrogen atoms, resemble aromatic compounds, however. The sixteen-membered ring, containing six double bonds, is *uniplanar* as shown by X-ray examination. The porphyrins are similar, four nitrogens of the phthalocyanine ring being replaced by four carbon atoms. The stability of these rings must therefore be interpreted along the lines now accepted for aromatic compounds.

Chelate Rings.[75] The term 'chelate' (from the 'chela' or great claw of crustaceans) was introduced by the late Sir Gilbert Morgan to describe groups which can form two links with a metal in a co-ordination complex thus producing a ring.[76] Well-known examples are ethylenediamine which gives rings of the type

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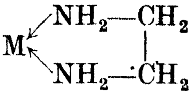
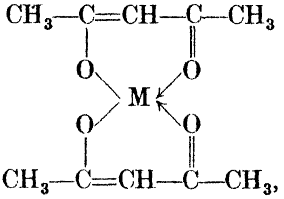
[73] See Drew, *Ann. Reports*, 1934, **31**, 146.

[74] *J.C.S.* 1934, 1016, and following papers; *Ann. Reports*, 1935, **32**, 359.

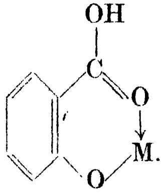
[75] See Sidgwick, *The Electronic Theory of Valency*, chap. xiv.



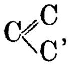
as in $[Co(en)_3]Cl_3$, the acetylacetone radical in metallic derivatives such as



and the salicylic acid residue in



The inclusion of the metal in a complex is indicated by the fact that it does not separate as kation, or by the absence of salt-like characters in the compound. A notable feature of these cyclic systems is the frequent occurrence of six-membered 'chelate' rings with two conjugated double linkages. Assuming the regular tetrahedral model (as in the simple Baeyer theory which, as pointed out above, may be accepted as a rough guide in predicting the stability of ring systems), the angle between the valencies of a saturated carbon atom is 109° 28′, while that between a single and a double bond,



$C\langle^{C}_{C}$, is 125° 16′; a calculation made on this basis leads to the result that a six-membered ring with two double linkages has no strain and should therefore be very stable. The predominance of 'chelate' rings of this particular type is not surprising, therefore, while the presence of *conjugated* double linkages will lead to a further increase of stability owing to mesomerism. 'Chelate rings' containing a hydrogen bond are dealt with in the following chapter.

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[76] *J.C.S.* 1920, **117**, 1457.

XV

APPLICATIONS OF KINETIC METHODS TO STEREOCHEMICAL PROBLEMS

REFERENCE has already been made to the use of modern physical methods in the attack upon problems of stereochemistry, and examples have been given also of the application of stereochemical observations in the elucidation of reaction mechanisms.[1] In certain other instances considerable light has been thrown upon stereochemical problems by the use of kinetic methods of investigation. An outstanding example is found in the recent work of Ingold, Hughes, and their collaborators, who have been able to correlate the steric course of substitution with reaction mechanism, thus making a substantial contribution to the understanding of the much-discussed phenomenon of Optical Inversion. The problem of Steric Hindrance has also been attacked by kinetic methods. These two subjects are dealt with below.

1. *The Walden Inversion*

The replacement of a group linked to the 'asymmetric' carbon atom of an optically active compound frequently leads to a racemic product; for example, hydrogen bromide reacts with *l*-mandelic acid to give inactive phenylbromoacetic acid. It is clear that, in this process of racemization, 50 per cent. of the compound undergoes inversion of configuration. In 1896 Walden, in the course of an investigation of optically active halogen-substituted succinic acids, observed instances where far more than 50 per cent., and even up to 100 per cent., of a compound became inverted during a reaction,[2] and many further examples of the 'Walden Inversion' have since been found by Emil Fischer, McKenzie, Pickard and Kenyon, and others. The observations which indicate inversion are of two types: (*a*) An optically active compound may be converted into its stereoisomeride by two replacements. Moreover, if this product is again subjected to the same two processes, the original stereoisomeride may be re-formed; this constitutes a complete 'optical cycle'. The example first observed by Walden was the following:

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[1] See especially Chaps. IX and XIII.

[2] *Ber.* 1896, 29, 133.

$$\begin{tikzcd}
\textit{l}\text{-chlorosuccinic acid} \arrow[r, "Ag_2O"] & \textit{l}\text{-malic acid} \arrow[d, "PCl_5"] \\
\textit{d}\text{-malic acid} \arrow[u, "PCl_5"] & \textit{d}\text{-chlorosuccinic acid} \arrow[l, "Ag_2O"']
\end{tikzcd}$$

A similar example, discovered by Emil Fischer during his work on amino-acids, was[3]

$$\begin{tikzcd}
\textit{d}\text{-}\alpha\text{-aminopropionic acid} \arrow[r, "NOBr"] & \textit{l}\text{-}\alpha\text{-bromopropionic acid} \arrow[d, "NH_3"] \\
\textit{d}\text{-}\alpha\text{-bromopropionic acid} \arrow[u, "NH_3"] & \textit{l}\text{-}\alpha\text{-aminopropionic acid} \arrow[l, "NOBr"']
\end{tikzcd}$$

In passing from *l*-chlorosuccinic acid to its stereoisomeride an inversion must have taken place at one stage or the other, and in the complete cycle two inversions must have occurred; the same applies to the second example, of course. It cannot be assumed, however, that the inversion occurs in the step (e.g. *l*-malic acid → *d*-chlorosuccinic acid) which actually leads to a change in the sign of rotation, for compounds of similar configuration do not always have rotations of the same sign; for example, we now know that *dextro*-rotatory ethyl lactate has the same configuration as *laevo*-rotatory lactic acid although their signs of rotation are opposite. The occurrence of inversion is therefore not established by the mere observation of a change in the sign of rotation, but only by the production of the stereoisomeride of the same compound. (*b*) The same replacement may give stereoisomeric products when the reagent or the conditions are varied. Walden observed the following example:[4]

$$\begin{tikzcd}
 & \textit{l}\text{-malic acid} \\
\textit{l}\text{-chlorosuccinic acid} \arrow[ur, "Ag_2O"] \arrow[dr, "KOH"'] & \\
 & \textit{d}\text{-malic acid}
\end{tikzcd}$$

Phosphorus pentachloride and thionyl chloride sometimes give products with opposite signs of rotation;[5] e.g.

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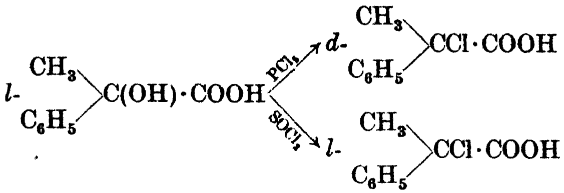
[3] *Ber.* 1907, **40**, 489.

[4] Ibid. 1897, **30**, 3146.

[5] McKenzie and Clough, *J.C.S.* 1910, **97**, 1016, 2564.



The work of Senter and his collaborators showed further that variation of the medium may lead to a different sign of rotation in the product of a given reaction;[6] for example, when ammonia reacts with optically active phenylchloroacetic acid an amino-acid of the same or opposite sign of rotation results, depending upon the solvent used. It is clear that inversion of configuration must have occurred in some of the examples quoted above, though not in others.

The interpretation of the mass of experimental observations relating to the Walden Inversion has proved a great stumbling-block to the organic chemist. Much difficulty has been experienced, for example, in the detection of the actual changes in which inversion takes place, and for a long time little progress was made in the determination of the conditions which govern its occurrence. These difficulties have been due very largely to the absence of reliable methods of relating sign of rotation to stereochemical configuration, but they have also arisen through a lack of knowledge of the mechanism of substitution at a saturated carbon atom. Of late years, however, notable progress has been made towards the solution of these problems.

A list of relative configurations was drawn up nearly thirty years ago by Frankland, on the basis of a statistical survey of the recorded effects of different reagents upon replacements at an asymmetric carbon atom,[7] and the conclusions there reached have been largely confirmed by recent work. Another list was drawn up five years later by Clough,[8] who assumed that similarity of configuration is accompanied by similarity in the effects of structural and external conditions; this appears to hold within prescribed limits,[9] but on the whole the results are less satisfactory than those of Frankland. Various other methods of a theoretical character have been used in the endeavour to relate structure to rotation.[10] A definite advance has been made in recent years by Kenyon, Phillips, and co-workers, who have employed a chemical method which has enabled them to establish a number of configurations with a good degree of certainty.[11] Their results are illustrated by the following scheme, which is typical of many series of transformations which they have carried out; the letters *d* and *l* above the formulae denote the observed signs of rotation.

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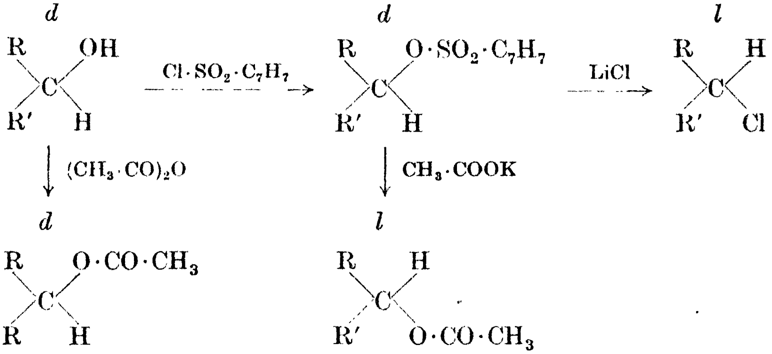
[6] *J.C.S.* 1915, **107**, 638; 1916, **109**, 1091, and later.

[7] Ibid. 1913, **103**, 713.

[8] Ibid. 1918, **113**, 526.

[9] See Freudenberg and Lux, *Ber.* 1928, **61**, 1083.

[10] See summary by Hughes, *Trans. Faraday Soc.* 1938, **34**, 202.



It may safely be assumed that, of all these replacements, only the reactions of the *p*-toluenesulphonate with acetate or chloride ions involve the rupture of one of the linkages of the asymmetric carbon atom, and therefore inversion is possible only in these two stages. Since the acetate obtained by direct acetylation of the secondary alcohol by acetic anhydride, a reaction not involving the asymmetric carbon atom, has the same sign of rotation as the alcohol, whereas that prepared by the reaction of acetate ion with the *p*-toluenesulphonate has the opposite sign, it may be concluded that inversion occurs in the latter replacement, and hence that the alcohol and the acetate having the same sign of rotation are alike in stereochemical configuration. By analogy this will apply also to the chloride. The correctness of the view that halide ion, like acetate ion, causes inversion is confirmed by the work of Hughes and his collaborators, who studied the replacement of a halide ion by one of the same kind, using isotopically distinguished halogen.[12] An organic halide in acetone solution was treated with a metallic halide containing the radioactive isotope of the halogen, and the rate of exchange of halogen (e.g. $RI + NaI^* = RI^* + NaI$, where I^* represents the radioactive isotope of iodine) was determined by measurement of the intensities of radioactivity of the alkyl halide or the metallic halide after known time-intervals. The velocity of racemization was found polarimetrically, and in the three cases examined the rates of exchange and racemization were equivalent within experimental error. The configurations arrived at by Kenyon and Phillips are doubtless correct, and it is the knowledge of these that has made possible the recent advances towards the elucidation of the conditions governing the occurrence or otherwise of the Walden Inversion.

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[11] *J.C.S.* 1923, **123**, 44; 1925, **127**, 399, 2564; 1929, 1700; 1933, 173; 1935, 1663.
[12] Ibid. 1935, 1525; 1936, 1173; 1938, 209.

Most of the earlier attempts to ascribe a mechanism to the Walden Inversion postulated the initial formation of an addition product.[13] The theories of Fischer,[14] Werner,[15] and Pfeiffer[16] were of this type; according to these views the attacking reagent became linked to the asymmetric carbon atom by 'residual affinity', and in the breakdown of the additive compound the new group might or might not take up the place vacated by the group detached. The more recent views of Meisenheimer[17] represent a development of the same conceptions. Numerous other suggestions have been made from time to time,[18] but many of these are not now of much interest. The view that the first step is an ionization, which is the reverse of the earlier conception of initial addition of the reagent, has been discussed by Lowry[19] and by Kenyon and Phillips.[20] The remaining alternative, viz. the simultaneous addition of one group and removal of the other, is in harmony with modern views of bimolecular substitution processes;[21] it was suggested in connexion with the Walden Inversion by G. N. Lewis,[22] and has appeared in the recent theories of Olson[23] and of Meer and Polanyi.[24]

Finally, Ingold, Hughes, and co-workers[25] have discussed the problem in the light of their two mechanisms of aliphatic substitution;[26] they employ the theory of simultaneous addition and dissociation in conjunction with that of initial dissociation. Theoretical considerations lead them to the conclusion that bimolecular substitutions (S_N2, S_E2) will invariably be accompanied by inversion, whereas unimolecular substitutions (S_N1, S_E1) will lead most commonly to inversion with considerable racemization, the actual result being in this case influenced by other circumstances. These conclusions are borne out by the results of kinetic and polarimetric studies of the replacement of halogen by hydroxyl or alkoxyl, the occurrence or otherwise of inversion in the changes examined being detected by the aid of the configurations established by Kenyon and Phillips.

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[13] For summary see *Ann. Reports*, 1911, **8**, 60.

[14] *Annalen*, 1911, **381**, 123.

[15] *Ber.* 1911, **44**, 873.

[16] *Annalen*, 1911, **383**, 123.

[17] Ibid. 1927, **456**, 126.

[18] For example, Gadamer, *Chem. Zeit.* 1912, **36**, 1327. Holmberg, *Ber.* 1926, **59**, 125. Rördam, *J.C.S.* 1928, 2447; 1929, 1282; 1930, 2017.

[19] *Deuxième Conseil de Chimie Solvay*, 1925.

[20] *Trans. Faraday Soc.* 1930, **26**, 451.

[21] See Chap. V, p. 71.

[22] *Valence and the Structure of Atoms and Molecules*, 1923, p. 113.

[23] *J. Chem. Physics*, 1933, **1**, 418.

[24] *Z. physikal. Chem.* 1932, B, **19**, 164.

[25] Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.C.S.* 1937, 1252. For summary see *Ann. Reports*, 1938, **35**, 218.

[26] See Chap. X.

A bimolecular substitution will lead to inversion because the attacking reagent approaches the asymmetric carbon atom on the side remote from the group which is replaced.[21] In a nucleophilic substitution by the unimolecular mechanism, however, the first step is the formation of a positive ion which loses its asymmetry and becomes flat;[27] substitution at either side will then occur with equal ease, giving a racemic product. The occurrence or otherwise of racemization thus provides a further criterion of reaction mechanism.[28] The experimental test of these deductions was made on several secondary halides. Their hydrolysis or alcoholysis normally occurs by the S_N1 and S_N2 mechanisms simultaneously,[26] but suitable adjustment of the experimental conditions may cause one or the other mechanism to take almost complete control, and hence the reaction by each mechanism can be examined. It has been found that the bimolecular hydrolysis and alcoholysis of β-*n*-octyl halides, $C_6H_{13} \cdot CHX \cdot CH_3$, of α-bromopropionic acid and of methyl α-bromopropionate occur with inversion of configuration and an almost quantitative preservation of optical activity. Extensive racemization accompanies the unimolecular hydrolysis of the β-*n*-octyl halides and also that of α-phenylethyl halides, but the racemization is nevertheless not complete and some optical activity is retained, the configuration being inverted. This is ascribed by Ingold and his collaborators to the shielding of the cation by the receding anion in such a manner that substitutions with inversion outnumber those in which the original configuration remains; inversion with considerable racemization is the obvious result. Hydrolysis by silver oxide or by soluble silver salts (e.g. $RCl+AgNO_3+H_2O = ROH+AgCl+HNO_3$) is comparable with homogeneous unimolecular hydrolysis. The alkyl halide adsorbed on the surface of the silver oxide or halide is attacked by a silver ion, also adsorbed, and the halogen removed; the resulting ion then reacts as in the S_N1 mechanism. In accordance with this view, the hydrolysis by silver oxide or nitrate of β-*n*-octyl and of α-phenylethyl halides gives in each case predominating inversion with extensive racemization.

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[27] Wallis and Adams, *J. Amer. Chem. Soc.* 1933, **55**, 3838. See also Shriner, Adams, and Marvel in Gilman's *Organic Chemistry*, 1938, vol. 1, p. 303.

[28] Compare p. 138.

The combination of kinetic and polarimetric methods of investigation has thus made it possible to link the steric course of a reaction with its mechanism, and hence to predict and interpret the influences of the factors by which mechanism is determined, viz. the structure of the reacting compound and the conditions under which the reaction occurs. The Walden Inversion is no longer an isolated and mysterious phenomenon; it now falls logically into its place in the general theoretical treatment of chemical reactions, a satisfactory state of affairs which has been arrived at by the application of kinetic methods to the solution of the problems involved. Only a relatively small portion of the field has as yet been covered in detail, but it is not too much to hope that continued and systematic investigation along lines similar to those which have enabled Ingold, Hughes, and co-workers to make their recent contribution will ultimately bring the whole subject into one clear and complete picture.

2. *The* Ortho-*Effect*

Marked differences in properties are frequently observed between benzene derivatives having groups in *ortho*-positions with respect to each other and the isomeric compounds where the groups are not so placed. This '*ortho*-effect' is probably not to be ascribed to the same cause in every instance, but whatever be its nature in individual cases it is clear that the relative positions of groups in *ortho*-substituted compounds often make possible the operation of some factor which is absent in the isomeric derivatives.

In a discussion of the physical properties of a number of phenols, Sidgwick and Callow pointed out[29] that those of the *ortho*-substituted compounds are frequently abnormal (when compared with the properties of the *meta-* and *para*-isomerides). The peculiarity is observed, however, only if the substituent group contains an electron-donating atom (e.g. oxygen of CHO, COOR, or NO_2), and the suggestion was made that a hydrogen bond is formed between this atom and the hydroxyl group. Salicylic aldehyde, for example, is represented as I (below) which, on modern views, indicates a state of resonance between II and III; *o*-nitrophenol is similarly represented as IV.

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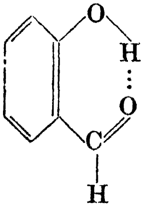
[29] *J.C.S.* 1924, **125**, 527. Compare Sidgwick, *Electronic Theory of Valency*, p. 147.

I



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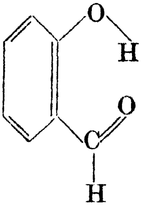
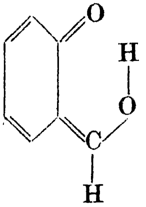
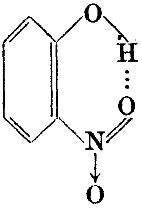


III



IV



The formation of the hydrogen bond is rendered possible by the relative positions of the oxygen atoms, which are thereby linked in a six-membered 'chelate ring' with two double bonds (the most frequent type of 'chelate ring'),[30] and the resonance is assisted by the electronic redistribution which is permitted by the conjugated double linkages. The process will clearly lead to a suppression of the characters dependent upon the hydroxyl group. For example, the solubility of the compound in hydrocarbons will be increased and its solubility in hydroxylic liquids such as water will be decreased; also, since the hydrogen is already acting as 'acceptor' atom, molecular association will be inhibited and an increased volatility will result. This is exactly what is observed when the properties of salicylic aldehyde or *o*-nitrophenol are compared with those of the isomeric *meta-* and *para*-substituted phenols. The position is the same, in fact, as that already described with reference to the enolic forms of β-diketones and β-ketonic esters.[31] Certain other *o*-substituted phenols in which the formation of a six-membered ring is not possible also differ very appreciably in volatility and solubility from their *m-* and *p*-isomerides, although not to the same extent as those referred to above. The formation of a five-membered ring is here postulated by Sidgwick and Callow, who represent *o*-chlorophenol as in V.

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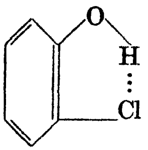
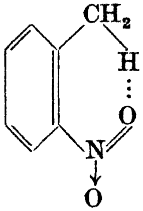
[30] See p. 234.

[31] p. 168.

V



VI



It is evident that such chelation depends upon the presence of an electron-donating atom; moreover, the atoms to be linked through hydrogen must be so placed that the hydrogen can become attached to either. This latter condition is apparently fulfilled best in the six-membered 'ring' with two double linkages and less completely in the five-membered 'ring', for in the latter case chelation occurs to a smaller extent than in the former. The physical properties of *o*-cresol and other *o*-alkyl substituted phenols give no indication of chelation. There are two reasons for this: (*a*) the difficulty of removal of a proton from its combination with carbon to take part in a process which is virtually an ionization, and (*b*) the fact that hydroxyl is predominantly electron accepting rather than donating. A neighbouring group of a powerfully electron-attractive character might, however, loosen the hydrogen of an alkyl group sufficiently to permit the formation of such a 'bond' with a suitably placed electron donor. Sidgwick and Callow[32] suggest that this may occur in *o*-nitrotoluene, which would then be written as VI (above).

The presence of a hydrogen bond in *ortho*-substituted phenols has been confirmed by spectroscopic investigations. Thus, the characteristic infra-red absorption of organic molecules containing a free hydroxyl group is absent in a number of compounds, including salicylic aldehyde, esters of salicylic acid, and *o*-hydroxyacetophenone,[33] and internal hydrogen bonding is indicated also by the Raman spectra of salicylic aldehyde and ethyl salicylate.[34] The phenomenon is not restricted to phenols, for there is evidence of hydrogen bond formation in compounds where an electron-donating group is situated in the *ortho*-position with respect to an acylamido-group. The work of von Auwers and others[35] showed that, whereas amides and anilides are normally associated in solution, there is little or no association in anilides where a nitro- or aldehyde-group is present in the *ortho*-position. Since the molecular association doubtless occurs through the hydrogen of the amido- or imido-group (for if this hydrogen is completely replaced the compound is unassociated), the natural inference to be drawn from this observation is that in the *ortho*-substituted anilide this hydrogen is already engaged in internal bond formation. Chaplin and Hunter[36] have recently demonstrated the absence of association in a number of other compounds, exemplified by *o*-nitroacylanilides, *o*-acetamidoacetophenone, and ethyl *o*-acetamidobenzoate, which are therefore to be represented in the following manner (VII, VIII, IX):

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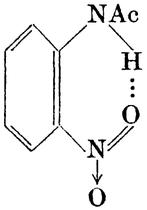
[32] Loc. cit., p. 538.

[33] Hilbert, Wulf, Hendricks, and Liddel, *J. Amer. Chem. Soc.* 1936, **58**, 548.

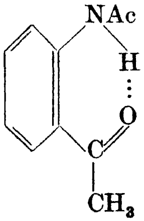
[34] Kahovec and Kohlrausch, *Z. physikal. Chem.* 1937, B, **38**, 119.

[35] For references see *Ber.* 1937, **70**, 966.

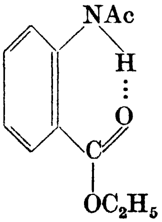
VII



VIII



IX



The considerable evidence of chelation in compounds where two suitable groups stand in *ortho*-positions with respect to each other suggests the possibility that similar processes may contribute to the familiar unreactivity of many *ortho*-substituted benzene derivatives, and, indeed, to many phenomena which have in the past been attributed to steric hindrance. The singular depression of chemical reactivity to which the '*ortho*-effect' gives rise appears to have first been recorded by Hofmann in 1872. He found that certain dialkylanilines with two substituents in *ortho*-positions refused to form quaternary salts when treated with alkyl halides under ordinary conditions;[37] this reaction is also retarded by *one ortho*-substituent.[38] A similar effect was observed, at quite an early date, in many other reactions, such as the hydrolysis of aromatic nitriles and acid amides[39] and the formation of oximes and phenylhydrazones by quinones and aromatic ketones.[40] A series of investigations by Victor Meyer, Sudborough, and their collaborators, from 1894 onwards, revealed a multitude of facts regarding the esterification of di-*ortho*-substituted benzoic acids, and the hydrolysis of their esters, chlorides, amides, and nitriles.[41] The acids gave no ester when their alcoholic solutions were either saturated with hydrogen chloride at 0° or treated by the Fischer-Speier method; even when the boiling solutions were saturated with hydrogen chloride for long periods of time the esterification was either not detectable (when the two groups in *o*-positions were NO_2, Cl, Br, or I) or very slight (with alkyl groups, OH or F). Moreover, the esters and other derivatives of these acids were unusually stable to hydrolytic reagents. The retardation of esterification and hydrolysis by *one* *ortho*-substituent has also been demonstrated,[42] and a single *ortho*-substituent inhibits almost completely the esterification of an aromatic nitrile by alcohol and hydrogen chloride.[43] The reactivity of a group in an *aliphatic* compound may also be greatly depressed by the presence of neighbouring substituents as shown, for example, by the order of velocities

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[36] *J.C.S.* 1937, 1114; 1938, 375, 1034.

[37] *Ber.* 1872, **5**, 704. Compare Fischer and Windaus, ibid. 1900, **33**, 345, 1967.

[38] See, e.g., Thomas, *J.C.S.* 1913, **103**, 594.

[39] Merz and Weith, *Ber.* 1883, **16**, 2886; Hofmann, ibid. 1884, **17**, 1915; Jacobsen, ibid. 1889, **22**, 1219; Claus *et al.*, *Annalen*, 1891, **265**, 364, and later papers.

$$CH_3\cdot COOH > CH_2X\cdot COOH > CHX_2\cdot COOH > CX_3\cdot COOH$$

for the esterification of *all* series of substituted acetic acids independent of the nature of X,[44] and by the different rates of esterification of *cis* and *trans* substituted acrylic acids.[45]

The strengths of aromatic acids and bases are also profoundly influenced by substituents in the *ortho*-position, and analogies are found in phenomena such as the greater strength of *allo*cinnamic than of cinnamic acid. All *o*-substituted benzoic acids are stronger than benzoic acid itself, and often very considerably stronger than their *m*- and *p*-isomerides. This is illustrated by the following thermodynamic dissociation constants.[46]

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[40] Kehrmann, *Ber.* 1888, **21**, 3315, and later; Hantzsch, ibid. 1890, **23**, 2773; V. Meyer, ibid. 1896, **29**, 835.

[41] See summary and full references given by Lloyd and Sudborough, *J.C.S.* 1899, **75**, 580. For a summary of the literature on the *ortho*-effect see Cohen, *Organic Chemistry*, Fifth Edition (Edward Arnold & Co., 1928), vol. i, chap. v.

[42] Goldschmidt, *Ber.* 1895, **28**, 3218; Kellas, *Z. physikal. Chem.* 1897, **24**, 221; Kindler, *Annalen*, 1928, **464**, 278.

[43] Pfeiffer *et al.*, ibid. **467**, 158.

[44] Sudborough and Lloyd, *J.C.S.* 1899, **75**, 467.

[45] Sudborough *et al.*, ibid. 1898, **73**, 81; 1905, **87**, 1840.

[46] From tables given by Dippy, *Chem. Reviews*, 1939, **25**, 204.

10^5K *for substituted Benzoic Acids*

Benzoic acid = 6·27

	OH	OCH_3	CH_3	F	Cl	Br	I	NO_2	OC_6H_5
o-	105·0	8·06	12·35	54·1	114·0	140·0	137·0	671·0	29·7
m-	8·3	8·17	5·35	13·65	14·8	15·4	14·1	32·1	11·2
p-	2·9	3·38	4·24	7·22	10·5	10·7	..	37·6	3·00

Very few values for di-*ortho*-substituted benzoic acids are available, but in at least two cases (2:6-dihydroxy and 2:6-dinitro) the presence of a second *o*-substituent leads to a further large increase in the dissociation constant. Groups in the *o*-position *decrease* the strengths of anilines[46] and confer increased stability upon benzaldehyde cyanohydrins.[47]

Victor Meyer attributed the *ortho*-effect to steric hindrance. This view was based upon the observation that the influence of a group in the *ortho*-position appears to be dependent upon its size (as measured, according to Meyer, by the sum of the weights of the atoms present) rather than upon its chemical characters; for example, *o*-F is not comparable with the other halogens. Meyer also pointed out that no *ortho*-effect is observed if the reacting group is separated from the nucleus by one or more carbon atoms; this is evident, for example, in the dissociation constants and esterification velocities of *o*-substituted phenylacetic and cinnamic acids and in the velocities of hydrolysis of their esters.[46,48] Flürscheim applied Meyer's view to the interpretation of the strengths of *ortho*-substituted acids by supposing that the steric hindrance opposed the recombination of the ions but not their dissociation.[49] There is, however, no simple relationship, even of a qualitative nature, between the relative effects of groups in the *o*-position and their weights or volumes (for example, NO_2 is usually more effective than Br or I in spite of its smaller size). While, therefore, steric retardation may frequently be an important factor (compare in this connexion the restricted rotation in *o*-substituted diphenyls and analogous compounds), the problem of the *ortho*-effect is one of great complexity, and the observations cannot be explained completely in terms of a purely geometrical effect.[50]

It is significant that in all cases where the *ortho*-effect has been observed to operate powerfully, the reacting group contains an atom which is known to be a powerful electron donor, e.g. COR, COOR, NR_2. Olivier finds, for example, that while the hydrolysis of *benzoyl* chloride is very greatly retarded by two bromine atoms in *ortho*-positions, that of *benzyl* chloride is not; taking the velocity of hydrolysis of the unsubstituted compound as unity in each case, those of 2:6- and 3:5-dibromo*benzoyl* chlorides are 0·0112 and 13·5, and those of the corresponding *benzyl* chlorides are 0·12 and 0·07 respectively.[51] The *ortho*-effect is never detected, indeed, in the reactions of substituted benzyl chlorides,[52] nor is it evident in the dissociation constants of the phenylboric acids, $X\cdot C_6H_4\cdot B(OH)_2$.[53] Moreover, *o*-substituted phenols are not more strongly acidic than their *m*- and *p*-isomerides, nor are they appreciably less reactive;[54] it may be noted that hydroxyl is predominantly an electron-acceptor (through its hydrogen atom), and that the hydrogen bond in the formulae written by Sidgwick and Callow would not be expected to have much influence upon the dissociation of the phenol or upon the electron-availability of the oxygen.

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[47] Lapworth and Manske, *J.C.S.* 1928, 2533.

[48] Meyer and Sudborough, *Ber.* 1894, 27, 1580; Kindler, ref. 42.

[49] *J.C.S.* 1909, 95, 725.

[50] Compare Davis, *J.C.S.* 1900, 77, 33; Kindler, ref. 42.

This apparent connexion of the *ortho*-effect with electron-donating atoms confirms the suspicion that it may have its origin in a chelation process. The high dissociation constant of salicylic acid (as contrasted with that of *o*-methoxybenzoic acid) has, in fact, been interpreted by Branch and Yabroff as due to the formation of a hydrogen bond between the hydroxyl and carboxyl groups;[55] this is, of course, an obvious extension of the views of Sidgwick and Callow. The positions of the atoms in salicylic acid are particularly favourable for the occurrence of such a process since it leads to a six-membered chelate ring with two conjugated double linkages. It may be suggested further that the chelation will occur in the anion $R\cdot COO^{\ominus}$ to a far greater extent than in the undissociated acid, and that the high dissociation constant therefore arises from the resulting increased stability of the ion (since the hydrogen bonding is a resonance process) and the decreased electron-availability of the oxygen atoms. The anion of salicylic acid is probably to be represented, therefore, by

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[51] *Rec. trav. chim.* 1929, **48**, 227.

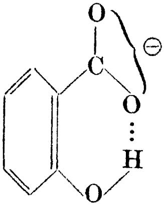
[52] See, e.g., Olivier, ibid. 1930, **49**, 697; Bennett and Jones, *J.C.S.* 1935, 1815.

[53] Branch *et al.*, *J. Amer. Chem. Soc.* 1934, **56**, 937, 1850, 1865.

[54] e.g. Boyd *et al.*, *J.C.S.* 1914, **105**, 2117; 1915, **107**, 1538; 1919, **115**, 1239; Burkhardt *et al.*, ibid. 1936, 17. The influences recorded by Davis (ref. 50) in the reactions of alcohols with 1-substituted β-naphthols are probably inductive effects.

[55] *J. Amer. Chem. Soc.* 1934, **56**, 2568.

X, a resonance state between the structures XI and XII. W. Baker[56] points out the probability that the further large increase in strength found in 2:6-dihydroxybenzoic acid ($K = 5\times 10^{-2}$) is due to the formation of hydrogen bonds by *both* oxygen atoms of carboxyl (which are, of course, actually equivalent). Sidgwick and Callow's suggestion regarding the possibility of chelation in *o*-nitrotoluene (VI, p. 243) may probably be extended to explain the relatively high dissociation constant of *o*-toluic acid,[57] the anion of which would then be written as XIII (above). The dissociation constants of *o*-nitro- and the *o*-halogeno-benzoic acids are considerably greater than those of their isomerides, but this appears to be due to the short distance from which the inductive effect of the group operates, for the logarithms of the dissociation constants of the isomeric acids of each series are related linearly to the values of the electrostatic potential (and also to those of the field intensity due to the C—NO_2 or C—Hal dipole (these are calculated from the dipole moments of the appropriate substituted benzenes).[58] The corresponding anilines and phenols show similar relationships.[59] The strength of *o*-methoxybenzoic acid is probably to be interpreted in the same manner, the inductive effect of methoxyl (—I), operating at short range, more than balancing the mesomeric effect which is responsible for the low dissociation constant of *p*-anisic acid.[60] The very much greater strength of salicylic acid, and the increase in strength conferred by *o*-methyl (a +I group), make necessary the chelation hypothesis outlined above, however; this applies also to the basic strength of *o*-toluidine. A similar view has been put forward to explain a rise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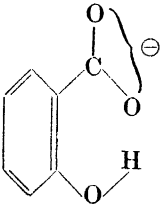
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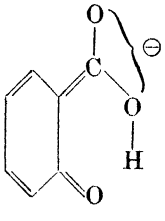
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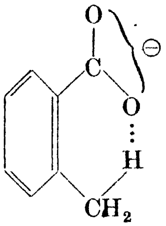
XIII

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[56] *Nature*, 1936, 137, 236.

[57] Dippy, Evans, Gordon Lewis, and Watson, *J.C.S.* 1937, 1421.

[58] Jenkins, ibid. 1939, 640.

[59] Ibid., p. 1137.

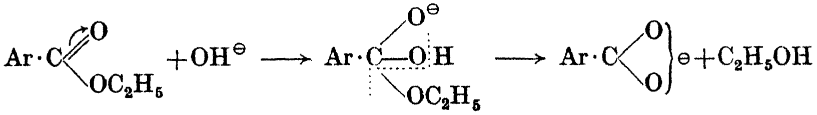
[60] See Chap. VI, p. 89.

in dissociation constant in passing from propionic acid to *n*-butyric acid in the saturated aliphatic series.[61]

The inadequacy of the 'geometrical steric hindrance' interpretation of the *ortho*-effect was emphasized by the discovery that the retardation of chemical reactions by groups in the *ortho*-position is in some cases associated with a high energy of activation. Peacock has found, for example, that the values of *E* for the reaction of *o*-toluidine with benzyl chloride and with 2:4-dinitrochlorobenzene are distinctly higher than the corresponding values relating to *m*- and *p*-toluidines,[62] and Hinshelwood and Legard's study of the esterification of *o*-nitrobenzoic and *s*-trimethylbenzoic acids has revealed a considerable increase in *E*, and an accompanying rise in the value of the *P* factor of the kinetic equation, due to the presence of the groups in *o*-positions.[63] The acid hydrolysis of ethyl *o*-nitrobenzoate shows the same features.[64] A purely geometrical effect would lead to a low velocity by reducing *P* rather than by increasing *E*.

Kinetic studies of the effects of a whole series of *ortho*-substituents have recently been carried out for two reactions of quite different types, viz. the addition of methyl iodide to dimethylanilines ('Menschutkin Reaction') in absolute methyl alcohol[65] and the alkaline hydrolysis of ethyl benzoates in 85 per cent. ethyl alcohol,[66]

$$\mathrm{Ar{\cdot}N(CH_3)_2 + CH_3I \longrightarrow [Ar{\cdot}N(CH_3)_3]I}$$



$$\mathrm{Ar{\cdot}C\overset{\nearrow O}{\underset{\searrow OC_2H_5}{}} + OH^{\ominus} \longrightarrow Ar{\cdot}C\overset{O^{\ominus}}{\underset{OC_2H_5}{—}}OH \longrightarrow Ar{\cdot}C\left\langle{O \atop O}\right\}^{\ominus} + C_2H_5OH}$$

In both cases substituents in the *m*- or *p*-position change only the energy of activation, leaving *P* practically constant;[67] electron-attractive groups (e.g. NO_2, Halogens) raise *E* for the Menschutkin reaction and lower it for the hydrolysis. The effect of moving a given substituent from the *para*- to the *ortho*-position is shown in the table below, where $E_0 - E_p$ represents the difference in the energies of activation and P_0/P_p the ratio of the values of the non-exponential term of the kinetic equation for the reactions of isomeric *ortho-* and *para*-substituted compounds.

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[61] See p. 99.

[62] *Nature*, 1932, **129**, 57; Singh and Peacock, *J. Physical Chem.* 1936, **40**, 669.

[63] *J.C.S.* 1935, 587.

[64] Timm and Hinshelwood, ibid. 1938, 862.

[65] Evans, Watson, and Williams, ibid. 1939, 1348.

[66] Evans, Gordon, and Watson, ibid. 1937, 1430.

[67] See Chap. V.

Relative Effects of Groups in o- *and* p-*positions*

Group	*Menschutkin Reaction*		*Alkaline Hydrolysis*	
	$E_o - E_p$	P_o/P_p	$E_o - E_p$	P_o/P_p
F	400	1	−300	1·0
OC_6H_5	1,100	3	..	..
OCH_3	1,900	9	..	..
Cl	3,700	40	−1,100	0·1
CH_3	6,600	250	−200	0·2
C_6H_5	6,200	400	..	..
NO_2	..	..	−300	0·04

A striking feature of the results is the complete absence of an '*ortho*-effect' for the fluoro-compounds. The influence of *o*-F is almost identical with that of *p*-F, and this is quite probably connected with the inability of fluorine to expand its valence group beyond eight electrons: it is not possible for the fluorine atom in the *ortho*-position to interact in any way with the unshared electrons of the trivalent nitrogen or carbonyl oxygen. In the Menschutkin reaction, all the remaining *ortho*-substituted compounds give higher energies of activation and higher values of the P factor than those found for their *para*-isomerides. This is illustrated graphically in Fig. 22, where E is plotted against $\log k$; reactions with the same P factor give points falling on the theoretical straight line of slope $-2{\cdot}303RT$, and the magnitude of an increase in P is indicated by the horizontal distance of the point from the theoretical line.[67] The largest effects are given by o-C_6H_5 and o-CH_3, which lead to energies of activation more than 6,000 calories higher than those for the isomeric *p*-compounds, and also to greatly increased values of P (by factors of 400 and 250 respectively). The remaining groups give appreciable though smaller effects, and the simultaneous rise in E and in P, found throughout, is reminiscent of that observed by Hinshelwood for esterification and acid hydrolysis in *ortho*-substituted compounds. The results for alkaline hydrolysis are illustrated in Fig. 14 of Chapter V.[68] The differences between the energies of activation for *ortho-* and *para*-substituted compounds are here relatively small, and the former now give the *lower* values; with the exception of fluorine, all the groups examined lead to a *decreased* value of P when they are in the *ortho*-position.

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[68] p. 77.

It is quite evident that these observations cannot be interpreted on the basis of a purely geometrical steric hindrance as envisaged by Victor Meyer; such a view would leave the high values of E and P unexplained, and, moreover, the relative effects of the different groups bear no relationship whatsoever to their volumes or weights.

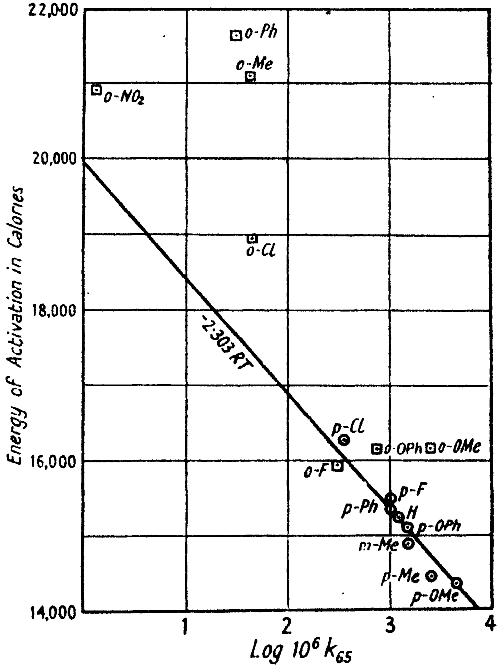
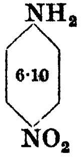
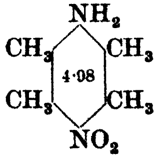
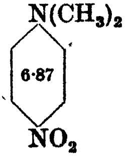


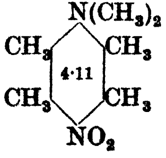
FIG. 22

Recent measurements of the dipole moments of a number of durene derivatives by Ingham and Hampson[69] have indicated a reduction in the mesomeric effect of an amino- or a dimethylamino-group by methyl groups situated in o-positions. The values of the moments (Debye units) in the centre of the formulae below are typical of their results.









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[69] *J.C.S.* 1939, 981.

They express the view that the o-CH_3 groups prevent the system from taking up a planar configuration, thus reducing the mesomerism, and it has further been suggested[70] that this factor is responsible for many of the peculiarities exhibited by compounds having o-substituents. For example, o-CH_3, o-Cl, and o-OCH_3 have been found to render the p-position of dimethylaniline less reactive,[71] an observation which could be interpreted by postulating the reduction of the mesomeric effect (and, by implication, the electromeric effect also), whatever be the cause. The addition of methyl iodide to dimethylaniline, however, depends upon the reactivity of the unshared electrons of the nitrogen atom (hence the unfavourable effect of electron-attractive groups in the nucleus), and a reduction of the mesomeric effect of $—N(CH_3)_2$ would give them additional freedom; the energy of activation would therefore be decreased, whereas *ortho*-substituents actually lead to an increased value of E. The lack of any connexion between the relative effects of groups and their volumes is also unfavourable to any view which postulates a steric inhibition either of mesomerism or of any other factor. Nevertheless, the views of both Meyer and Hampson will doubtless find a place in a complete and comprehensive interpretation of all the phenomena observed in connexion with *ortho*-substituted compounds.

The kinetic results outlined above appear to be interpreted most satisfactorily by an extension of Sidgwick and Callow's view of hydrogen bonding. In the phenols to which this view was applied originally, there is evidence of chelation under ordinary conditions; the hydrogen bond is present in the resting state of the molecule. The ionizable character of the phenolic hydrogen may be held responsible for this (and a similar remark applies to the anilides studied by Chaplin and Hunter). But there is no reason to suppose that the o-substituted dimethylanilines and benzoic esters are in general chelated, except in special instances such as ethyl salicylate. When the attacking reagent approaches one of these molecules, however, the whole system becomes energized as it climbs the 'energy valley' to the 'pass' which represents the transition state, and under these conditions (which are totally different from those existing in the resting state of the molecule) it is not unlikely that the unshared electrons of trivalent nitrogen or carbonyl oxygen may interact with a methyl or phenyl group situated in the *ortho*-position, forming a hydrogen bond. This is, in reality, an electronic expression of views previously put forward by von Braun[72] and by Kindler;[42] it is identical with the suggestion advanced by Evans to explain the rather high energy of activation found in the bromination of propiophenone.[73] In the case of the dimethylanilines, the electrons of the nitrogen will thus be made less available for reaction with the methyl iodide, and the energy of activation will consequently be raised. The effects of *o*-Cl, *o*-OCH_3, and *o*-OC_6H_5 are much smaller than those of *o*-CH_3 and *o*-C_6H_5; it may be supposed that these groups interact with the unshared electrons of the nitrogen in such a way that the latter are subjected to a constraint without the actual formation of a bond. In the ester complex, the interaction will be between the group and the unshared electrons of the carbonyl oxygen, whereas the attack of the reagent (hydroxyl ion) is at carbon, and so the energy of activation is not changed a great deal; the chelation process may assist the electromeric change $\overset{\frown}{C{=}O}$, thus reducing E a little. Esterification will show the same effects as the Menschutkin reaction does: the attack of the acid catalyst at carbonyl oxygen will be rendered less easy, and E will therefore be raised. The changes in the value of the P factor are less easy to account for, but an interpretation may perhaps be found in considerations of the following type. If the nitrogen atom of a dimethylaniline becomes the electron-donator in a chelation or similar process, it will gain a fractional positive charge (it is somewhat positive originally, owing to mesomerism). In the ester complex the carbonyl oxygen which provides the electron pair for such a process is originally negative, and it will transfer a portion of this charge. The following formulae (for the *o*-CH_3 compounds) make this clear:

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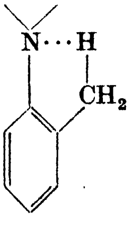
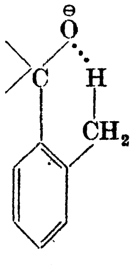
[70] Baddeley, *Nature*, 1939, **144**, 444.

[71] von Braun, *Ber.* 1916, **49**, 1101.





The chelation process thus causes a redistribution of charges, by which that part of the complex upon which the reaction depends becomes more charged in the case of the dimethylanilines and less charged in the case of the esters. It is known that a relatively high *P* value is characteristic of reactions involving either an ion or a charged catalyst;[74] the charge may tend to stabilize the complex so that it is better able to exist while the processes leading to the completion of the reaction are taking place. The effect of chelation upon that part of the complex where these processes must occur is thus in the direction which will lead to a higher *P* factor for the Menschutkin reaction and a lower value for the hydrolysis. The process will also reduce the mesomeric and electromeric effects of the dialkylamino-group, thus accounting for the decreased reactivity of the *p*-carbon atom.

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[72] loc. cit., *Ber.* 1918, 51, 282.

[73] See p. 98.

It is not suggested that the interaction of the unshared electrons of trivalent nitrogen or carbonyl oxygen with a group standing in the *ortho*-position occurs at any time except during the passage of the reacting system over the 'energy pass'. Thus, the peculiarities of the reactions of *ortho*-substituted compounds need not extend to equilibria, and it is not surprising that the strengths of most *o*-substituted acids and bases appear to show no effects which are not also found in the *p*-isomerides,[75] whereas the reactions of the same and similar compounds indicate a strong '*ortho*-effect'. In reactions we are dealing with the highly energized transition complex, whereas equilibria are concerned with two resting states, and the factors which govern the former are quite different from those determining the latter.

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[74] Hinshelwood, *Trans. Faraday Soc.* 1938, **34**, 138.

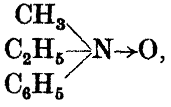
[75] See p. 248.

XVI

STEREOCHEMISTRY OF ELEMENTS OTHER THAN CARBON

A FEATURE of the advances in stereochemistry during the twentieth century has been the extension of the tetrahedral conception of the carbon atom to other elements; the first demonstration of optical activity due to an 'asymmetric' atom other than carbon dates from 1899, when Pope and Peachey resolved an ammonium salt in which the four radicals linked to the nitrogen atom were different. Stereochemical investigations of the classical type have given many important results, and the applications of X-ray and other physical methods have added very greatly to our knowledge of the directions of the valencies of many elements. The general conclusion to be drawn from the results is that four covalencies are directed tetrahedrally in many, perhaps the majority of cases, but that a planar arrangement is found in a number of examples. Six covalencies are always directed octahedrally as far as is known.

A short summary of the subject is given here. For fuller details the reader is referred to one of the larger treatises.[1]

Four Covalencies with Tetrahedral Configuration. The distinction between covalent and electrovalent linkages makes it clear that, while four groups in an ammonium salt are bound to nitrogen by directed valencies, the fifth occupies no fixed position; from the stereochemical point of view, therefore, only the four covalently bound groups enter into consideration. The tetrahedral disposition of these groups was suggested by van 't Hoff, and as early as 1891 Le Bel claimed to have observed a feeble optical activity in a solution of methyl-ethyl-propyl-*iso*butyl-ammonium chloride which had been submitted to the action of penicillium glaucum (Pasteur's biochemical method of resolution). The definite resolution of an ammonium salt was first achieved in 1899 by Pope and Peachey who obtained the optical isomerides of a phenyl-benzyl-allyl-methyl-ammonium salt,[2] and a considerable number of similar resolutions were carried out subsequently by H. O. Jones, Wedekind, and others. These were followed by Meisenheimer's separation of methyl-ethyl-aniline oxide,  $(CH_3)(C_2H_5)(C_6H_5)N \rightarrow O$, into its active components,[3] and the tetrahedral configuration of the valencies of four-covalent nitrogen was finally demonstrated by Mills and Warren,[4] who resolved a spirocyclic ammonium salt of the formula

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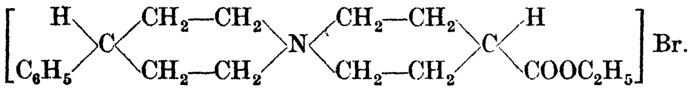
[1] See, for example, article by Shriner, Adams, and Marvel in Gilman's *Organic Chemistry*, New York, 1938, vol. 1, p. 327. Also, Sidgwick, *The Covalent Link in Chemistry* (Cornell University Press, 1933), chap. vi.

[2] *J.C.S.* 1899, 75, 1127.



$$\left[\begin{matrix} H \\ C_6H_5 \end{matrix} \!\!>\! C \!<\! \begin{matrix} CH_2{-}CH_2 \\ CH_2{-}CH_2 \end{matrix} \!>\! N \!<\! \begin{matrix} CH_2{-}CH_2 \\ CH_2{-}CH_2 \end{matrix} \!>\! C \!<\!\! \begin{matrix} H \\ COOC_2H_5 \end{matrix} \right] Br.$$

Other configurations were definitely excluded by the dissymmetry of this compound. The resolution of compounds containing four-covalent phosphorus or arsenic (e.g. methyl-ethyl-phenyl-phosphine oxide) has also been accomplished.[5] If the valencies of nitrogen, phosphorus, and arsenic retain their relative positions in compounds where these elements are three-covalent, these should also have dissymmetric molecules when the three attached groups are different; no example of optical activity has been found, however, in spite of many attempts to resolve such compounds.[6] Nevertheless, chemical evidence (e.g. the isomerism of the oximes) indicates a non-planar configuration for the valencies of nitrogen, and the dipole moments of ammonia, hydrazine, phosphine, arsine, and the trichlorides of phosphorus, arsenic and antimony, and also observations of infra-red spectra and the X-ray examination of the crystal of solid ammonia, lead to the conclusion that the three atoms linked to nitrogen, phosphorus, arsenic, or antimony occupy three angular points of a tetrahedron with the nitrogen or other atom at the apex. This conclusion is supported by the known facts regarding other elements in the three-covalent state (see below). The failure of all attempts at resolution is perhaps due to very easy racemization. It is suggested that the nitrogen atom, for example, can pass readily through the plane of the attached groups to give the optical isomeride (thus

[3] *Ber.* 1908, **41**, 3966.

[4] *J.C.S.* 1925, **127**, 2507. Compare Mills *et al.*, ibid. 1927, 2613.

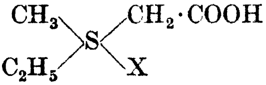
[5] Meisenheimer and Lichtenstadt, *Ber.* 1911, **44**, 356; Mills and Raper, *J.C.S.* 1925, **127**, 2479.

[6] For historical summary, see Gilman's *Organic Chemistry*, ref. 1. A summary of the present position and references to recent papers are given by Maitland, *Ann. Reports*, 1939, **36**, 239.

bringing about racemization); the energy of activation for this process is calculated to be only about 6,000 calories,[7] whereas detectable resolution is likely to be achieved only if the value is not less than 20,000 calories. Such a view is supported by observations of the infra-red spectrum of ammonia.

Of the elements of the carbon group, silicon and tin have both been shown to give rise to optical activity when linked to four different groups; some thirty years ago Kipping and co-workers resolved certain silico-ethers and silicanes having an 'asymmetric' silicon atom,[8] while Pope and Peachey had previously followed up their successful resolution of four-covalent nitrogen compounds by the observation of optical activity in methyl-ethyl-propyl-tin iodide.[9] The tetrahedral configuration of the valencies of the elements in this group has been confirmed by X-ray measurements on compounds such as the tetrahalides and tetraphenyls.[10]

The tetrahedral disposition of the valencies of four-covalent oxygen was demonstrated by Bragg and Morgan;[11] an X-ray study of basic beryllium acetate, $Be_4O(O\cdot COCH_3)_6$, showed that the oxygen atom is situated at the centre of a tetrahedron with the beryllium atoms at the corners and the acetate groups spanning the edges. In *divalent* oxygen the valencies retain their directions to a greater or less extent, as shown by the 'triangular' configuration of water.[12] The stereochemistry of the remaining elements of the oxygen sub-group has been studied by classical methods. For example, Pope and his collaborators[13] have resolved compounds of the type



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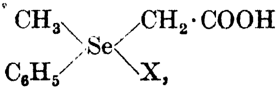

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[7] Manning, *J. Chem. Physics*, 1935, **3**, 136. A more recent computation, however (Kincaid and Henriques, *J. Amer. Chem. Soc.* 1940, **62**, 1474), has given the values 11,000 calories for ammonia (but the authors regard 8,000 calories as the probable correct value) and 15,000 calories for trimethylamine. These are still well below that needed for successful resolution, but the values found by these authors for trivalent phosphorus compounds are such as to lead them to the conclusion that these compounds could be resolved if the chemical difficulties were overcome. They obtain very high values for sulphonium compounds, which are resolvable (see above).

[8] *J.C.S.* 1907, **91**, 209, 717; 1908, **93**, 457, 2090; 1910, **97**, 755.

[9] *Proc. Chem. Soc.* 1900, **16**, 42, 116.

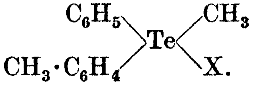
[10] e.g. Dickinson, *J. Amer. Chem. Soc.* 1923, **45**, 958; George, *Proc. Roy. Soc.* 1927, **113 A**, 585.

[11] *Proc. Roy. Soc.* 1923, **104 A**, 437.

[12] See p. 58.

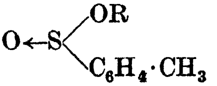
[13] Pope and Peachey, *J.C.S.* 1900, **77**, 1072; Pope and Neville, ibid. 1902, **81**, 1552. Compare Smiles, ibid. 1900, **77**, 1174; Balfe, Kenyon, and Phillips, ibid. 1930, 2554.

where X is the anion of a strong acid. A doubt existed in the case of tellurium, owing to the reported preparation of geometrical isomerides (which would indicate a uniplanar structure), but this element fell into line with the others when Drew proved that such geometrical isomerides did not exist,[14] and Lowry and Gilbert[15] were able to detect optical activity in a compound



An interesting feature of these observations was the fact that one of the four groups attached to the sulphur, selenium, or tellurium atom is ionizable. All these compounds are actually of the type [Mabc]X; it appears, therefore, that *three* of the groups occupying the corners of a tetrahedron remain in their positions in the absence of a fourth. A convincing demonstration of the correctness of this conclusion was provided by the resolution of sulphinic esters (I), sulphoxides (II), and a sulphonylimine (III) by Kenyon and Phillips:[16]

I



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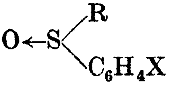
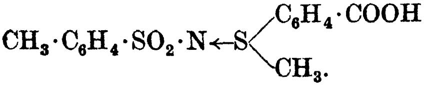


III



In addition to giving information regarding the arrangement of the groups around the central atom, this work also demonstrates the presence of a co-ordinate linkage, for dissymmetry would be impossible if the sulphur atom were doubly linked to oxygen or nitrogen. It also renders more probable the tetrahedral configuration of the valencies of trivalent nitrogen and allied elements (see above).

Results obtained by the classical methods of stereochemistry also indicate a tetrahedral configuration of valencies for boron and beryllium; in both cases optical activity has been detected in co-ordination compounds, such as the beryllium derivative of benzoylpyruvic acid:[17]

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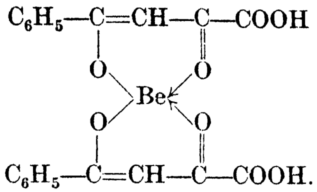
[14] *J.C.S.* 1929, 560.

[15] Ibid., p. 2867.

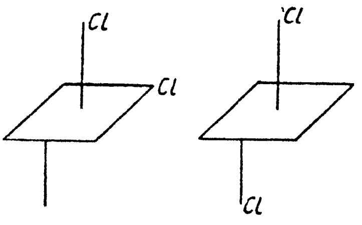
[16] Ibid. 1925, **127**, 2552; 1926, 2079; 1927, 188.

[17] Mills and Gotts, ibid. 1926, 3121.



A similar result was claimed for the corresponding compounds of copper and zinc, but in the case of copper the correctness of the observation is now open to doubt (see later). The crystal structures of a number of ions have also indicated a tetrahedral disposition of the valencies of the central atom; for example, permanganates, perchlorates, pervanadates, and the ions $\mathrm{Zn(CN)}_4''$, $\mathrm{Cu(CN)}_4''$, and $\mathrm{Hg(CN)}_4''$. A tetrahedral disposition of four covalencies is thus very frequent, the directions being maintained to a very large extent when less than four groups are linked to an atom which can be four-covalent. Two double bonds, or a triple and a single link, as in CO_2, CS_2, C_2H_2, and HCN, of necessity give a rectilinear molecule.

Six-Covalent Elements. The arrangement of six groups at the angular points of an octahedron was first demonstrated by Werner,[18] and no exception has been found; so far as we know, the valencies of a six-covalent element are always disposed octahedrally. Werner's conclusion was based on the preparation of geometrical isomerides of co-ordination compounds such as $[\mathrm{Cl_2Co(NH_3)_4}]\mathrm{Cl}$ and $[\mathrm{Cl_3Co(NH_3)_3}]$, which could be represented



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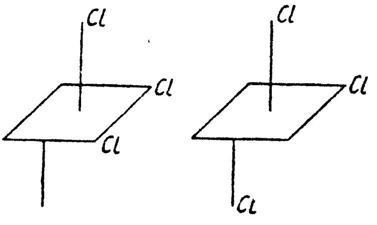

(NH_3 groups are here situated at the corners of the octahedron not occupied by chlorine atoms, and the metallic atom is at the centre of the solid figure). Elegant confirmation was obtained by the optical resolution of certain ethylenediamine complexes,[19] e.g.

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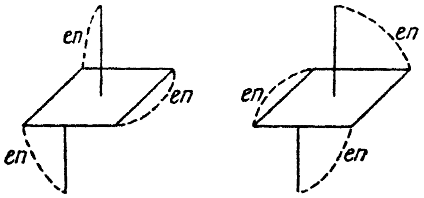
[18] *New Ideas on Inorganic Chemistry* (Longmans, 1911).

[19] *Ber.* 1911, **44,** 1887, and later. Ethylenediamine is a 'chelate' group, having a donor atom at each end; it therefore occupies two co-ordination positions. Dipyridyl, $NC_5H_4 \cdot C_5H_4N$, is similar.

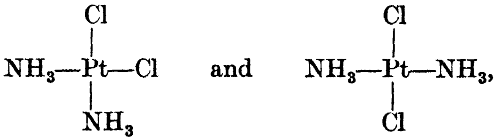
$[Co(NH_2\cdot CH_2\cdot CH_2\cdot NH_2)_3]Cl_3$, where the mirror-images may be written



Subsequent work by Werner and others has led to the resolution of compounds with the following elements in the six-covalent state: chromium, iron, nickel, ruthenium, rhodium, iridium, platinum, arsenic, and aluminium.[20] Crystal structure determinations have confirmed the octahedral configuration in every case so far examined.

The available evidence, therefore, provides no exception to the generalization that *six* covalencies are directed from the centre of an octahedron to its angular points.

Planar Configuration of Four Covalencies.[21] As early as 1893 Werner suggested that the valencies of four-covalent platinum lie in one plane.[22] This view made it possible to explain the existence of isomeric ammines of the type $[Cl_2Pt(NH_3)_2]$, which he represented as *cis* and *trans* stereoisomerides,



$$\begin{matrix} & Cl & \\ & | & \\ NH_3— & Pt & —Cl \\ & | & \\ & NH_3 & \end{matrix} \quad \text{and} \quad \begin{matrix} & Cl & \\ & | & \\ NH_3— & Pt & —NH_3, \\ & | & \\ & Cl & \end{matrix}$$

where the four groups lie in one plane with the platinum atom. The earlier observations of supposed isomerides among derivatives of four-covalent palladium were disproved,[23] but there is now a considerable body of evidence which shows that four groups covalently linked to platinum, palladium, or nickel are frequently coplanar.

(i) The existence of geometrical isomerism has been demonstrated conclusively; examples are found in the isomeric nickel derivatives of methyl-benzyl, methyl-*n*-propyl, and methyl-*n*-butyl glyoximes,[24] and the diglycine derivatives of palladium and platinum[25] (represented as I and II, where M = Pd or Pt).

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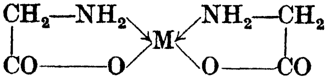
[20] For references see Sidgwick, ref. 1. A supposed case of six-covalent copper has been disproved (*J.C.S.* 1934, 1783).

[21] For excellent summaries, see Wardlaw, *Ann. Reports*, 1933, **30**, 106; 1934, **31**, 116; 1935, **32**, 160; 1936, **33**, 157; Cox and Wardlaw, *Science Progress*, 1938, **32**, 463.

[22] Ref. 18. Compare Hantzsch, *Ber.* 1926, **59**, 2761.

[23] Drew, Wardlaw, *et al.*, *J.C.S.* 1932, 1895; 1933, 1294.

[24] Sugden, ibid. 1932, 246; 1935, 621.



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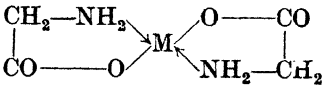
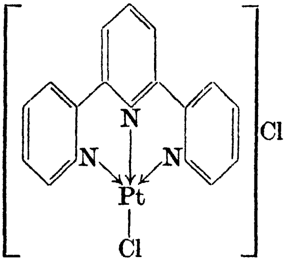


II

(ii) Morgan and Burstall have isolated a red crystalline salt [Pt(trpy)Cl]Cl, where (trpy) = 2:2′:2″-tripyridyl, in which a tetrahedral structure is impossible (III),[26] and Mills and co-workers have observed optical activity in certain substituted derivatives of $[Pt(en)_2]Cl_2$ and $[Pd(en)_2]I_2$ which would not be dissymmetric if the platinum or palladium valencies were disposed tetrahedrally (IV).[27]



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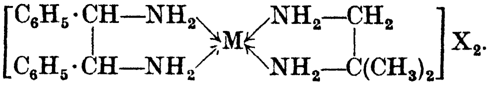

IV

(iii) In 1931 the possibility of a planar configuration of covalencies in the transitional elements was deduced by Pauling from wave-mechanical considerations.[28] On the basis of the Heitler-London theory of valency, he finds that the *normal* arrangement of six covalencies is octahedral and that of four covalencies tetrahedral. In the latter case the electrons which form the covalent bonds are usually those of the incomplete outermost group, and they belong only to the *s* and *p* sub-groups;[29] in the transitional elements, however, the electrons of the large group next to the outermost may take part in the process. These belong to the *s*, *p*, and *d* sub-groups, and Pauling arrives at the conclusion that a planar configuration is possible if *d* electrons take part in the formation of covalencies. Moreover, since the *d* electrons are mainly responsible for the paramagnetism of these atoms, this will be decreased if they are shared; hence the criterion of a planar configuration of valencies will be a reduced or zero paramagnetism in the resulting compound. Nickel, for example, which is paramagnetic in its simple salts, should become diamagnetic in its planar four-covalent compounds, and this is actually found to be the case; Sugden has shown that the nickel derivatives of dialkylglyoximes are diamagnetic.[24] The magnetic evidence relating to platinum and palladium is not so significant, for *all* compounds of these elements, both simple and complex, are diamagnetic. Diamagnetism does not persist throughout the compounds of four-covalent nickel, however, and Pauling's argument does not exclude a tetrahedral configuration.

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[25] Wardlaw, Cox, *et al.*, ibid. 1934, 1012.

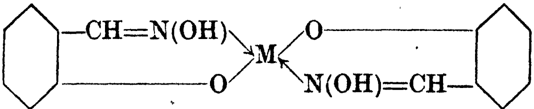
[26] Ibid. 1934, 1498.

[27] Ibid. 1935, 839; 1939, 1754.

[28] *J. Amer. Chem. Soc.* 1931, **53**, 1367.

[29] These terms are explained on p. 17. Magnetic phenomena are considered briefly on p. 63.

(iv) Definite evidence of the planar configuration of four-covalent nickel, palladium, and platinum has been obtained by X-ray measurements. In 1922 Dickinson examined potassium platino- and pallado-chlorides, K_2PtCl_4 and K_2PdCl_4, and concluded from his results that the four chlorine atoms are in one plane with the platinum or palladium atom, whereas analogous compounds of zinc, cadmium, and mercury [e.g. $K_2Zn(CN)_4$] show a tetrahedral arrangement.[30] Wardlaw, Cox, and their co-workers, in a series of X-ray investigations from 1932 onwards, have demonstrated a planar configuration in no less than fourteen derivatives of four-covalent platinum, palladium, and nickel,[31] viz. $[Pt(NH_3)_4]Cl_2$, $[Pd(NH_3)_4]Cl_2$, Magnus's green salt $[Pt(NH_3)_4][PtCl_4]$, $[Pt(en)_2]Cl_2$, $[Pd(en)_2]Cl_2$, $Pt(Me_2S)_2Cl_2$, $Pd(Me_2S)_2Cl_2$, the diglycine derivatives of palladium and platinum, the nickel and palladium derivatives of salicylaldoxime (V: M = Ni or Pd. The nickel compound is diamagnetic), and the dithio-oxalates of all three elements (VI: M = Ni, Pd, or Pt).



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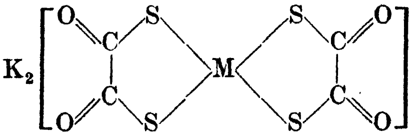

VI

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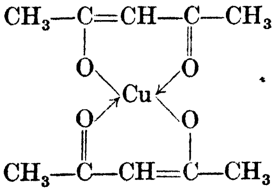
[30] *J. Amer. Chem. Soc.* 1922, **44**, 744, 2404.

[31] *J.C.S.* 1932, 1912, 2527; 1933, 1089; 1934, 182, 1012; 1935, 459, 1475.

The results of a chemical and X-ray examination of $Pd(NH_3)_2Cl_2$ and certain other palladium compounds by Mann and co-workers[32] are also in harmony with the same view. The valencies of platinum in the *platinic* compound $Pt(CH_3)_3Cl$[33] are arranged tetrahedrally, however, as are the nickel valencies in nickel carbonyl.[34]

Subsequent work, largely by Wardlaw, Cox, and their collaborators,[35] has provided further examples of two valency configurations for the same element. A planar configuration has been demonstrated for the *cupric* derivatives of salicylaldoxime and of certain β-diketones (e.g. VII, the acetylacetone derivative), for dipyridinocupric chloride $CuCl_2(py)_2$, for the cupric and argentic derivatives of picolinic acid (VIII), and for potassium auribromide $KAuBr_4$. $CuCl_2 \cdot 2H_2O$ is also planar,[36] as is diethyl-monobromo-gold[37] (IX). *Cuprous* and *argentous* compounds are tetrahedral, however, as is exemplified by potassium cuprocyanide $K_3Cu(CN)_4$, and by compounds of types X[35] and XI[38], while aurous compounds such as XII, like auric but



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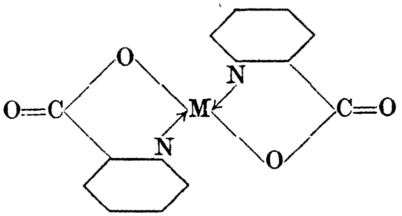
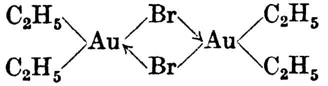


VIII



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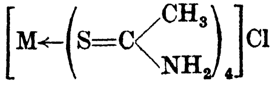
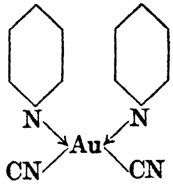


$$\left[M\leftarrow\left(S{=}C\begin{matrix}CH_3\\NH_2\end{matrix}\right)_4\right]Cl$$

X

$[(C_2H_5)_3As\rightarrow CuI]_4$

XI



XII

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[32] Ibid. 1935, 1642, and later.

[33] Cox and Webster, *Z. Krist.* 1935, **90**, 561.

[34] Brockway and Cross, *J. Chem. Physics*, 1935, **3**, 828.

[35] *J.C.S.* 1935, 731; 1936, 129, 775, 1635.

[36] Harker, *Z. Krist.* 1936, **93**, 136.

[37] Burawoy, Gibson, Hampson, and Powell, *J.C.S.* 1937, 1690.

[38] Mann, Purdie, and Wells, ibid. 1936, 1503.

unlike cuprous and argentous derivatives, are planar.[39] The four covalencies of tin and lead have a planar distribution in the double halides M_2SnX_4 (co-ordination compounds of SnX_2), potassium plumbo-oxalate, dithiourea lead chloride, lead salicylate, and the lead derivatives of benzoylacetone.[40] This contrasts with the tetrahedral configuration in stannic compounds and in lead tetraphenyl. Thallium is planar in thallous and tetrahedral in thallic compounds,[41] but there is evidence for both configurations in cobaltous compounds,[42] and for a planar disposition of valencies in both manganous and manganic compounds while the ion in manganates and permanganates is tetrahedral.[42] No satisfactory interpretation of all these observations has as yet been provided.

'At the present time experiment has to some extent outstripped theory and it is greatly to be hoped that the application of wave-mechanical methods will, in due course, show why, in certain cases, a change of principal valency results in a change of configuration and why, for example, this is not the case for 6- and 7-valent manganese. A further problem is whether any distinction can be made on theoretical grounds between the covalent and the co-ordinate link; it is significant that those compounds of bivalent cobalt which are planar involve co-ordinate links whereas only covalent bonds occur in the tetrahedral $[CoCl_4]''$. In its present state, theory cannot be completely reconciled with experiment in the matter of magnetic properties of co-ordination compounds; this is particularly the case, as Sugden has pointed out,[43] with copper and cobalt. Further work here appears very necessary.'[44]

It is possible at this stage, therefore, only to state the general results of experimental work; six-covalencies are invariably octahedral, but four-covalencies may be disposed either tetrahedrally or in a plane, the actual configuration not being determined by any known rules.

[39] Wardlaw *et al.*, *J.C.S.* 1939, 426.

[40] Idem, *Nature*, 1937, **139**, 71.

[41] *J.C.S.* 1938, 1886.

[42] Ibid. 1937, 1556.

[43] *Nature*, 1936, **137**, 543; 1937, **139**, 374.

[44] Cox and Wardlaw, *Science Progress*, 1938, **32**, 476.

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